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PRESENT STATUS OF THE ETIOLOGY OF PERNICIOUS ANEMIA *

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INTRODUCTION

To be among those who have received the award given annually in memory of Dr. John Phillips is an honor that I greatly cherish. Consequently, when President Fitz asked me to speak to you in connection with the subject for which this distinction was conferred upon me several years ago, I welcomed the opportunity because I hoped in this way to express some of my gratitude to the College. Happily enough, in the intervening years the advances in the understanding of the nature of pernicious anemia derived from many sources have been very great. Indeed, in the brief time at my disposal only the high lights of such progress can be delineated. Excellent review articles [1, 2, 3, 4, 5] are available for those interested in further details.

PERNICIOUS ANEMIA AS A CONDITIONED DEFICIENCY OF VITAMIN B_{12}

The recognition that pernicious anemia was in some sense a nutritional deficiency disease appeared at once from the classic demonstration by Minot and Murphy in 1926 of the effectiveness of liver feeding. This discovery confirmed Minot's long held surmise and proved to be an unexpected application of the basic principle established by Whipple's earlier observations of the quantitative influence of dietary components upon hemoglobin production in chronically bled dogs. So ended the era of descriptive study of pernicious anemia, which had defined its hematologic characteristics and had indicated the frequency of glossitis and of neural complications, as well

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as the almost invariable lack of gastric secretion. With the advent of liver therapy it appeared that the gastric dysfunction was unique in persisting unaltered despite improvement of the patient in all other respects.

Chiefly on the basis of this evidence, it was conceived that the lack of gastric juice "conditioned" a nutritional deficiency that did not exist for the normal individual. The correctness of this hypothesis was seemingly established when it was shown that beef muscle failed to promote hematopoiesis in pernicious anemia unless administered simultaneously [6] and at a pH between 3.5 and 7.0 [7] with normal human gastric juice. Because it thus appeared that such increased hematopoiesis required an interaction between the beef muscle and the gastric juice, these were designated, respectively, as the food (extrinsic) and gastric (intrinsic) factors of a preliminary reaction essential for the subsequent formation of the antipernicious anemia principle in the body.[7] If this is so, severe dietary disturbance, total operative removal of the stomach, or, for example, pronounced disturbance in absorptive capacity of the small intestine, should all result in a similar deficiency. Such appears to be the case, although these macrocytic anemias are variously designated and are likely to be due to deficiency of more than one substance unless achylia gastrica is the principal cause.

That the extrinsic factor, although present in beef muscle, liver, autolyzed yeast, eggs, milk and crude casein, is closely associated with but not identical to protein was later shown by the fact that exhaustive extraction of crude casein or of beef muscle proteins rendered them hematopoietically inert.[8] This further supported the earlier suspicion, based upon observations with autolyzed yeast, that the extrinsic factor might be a member of the vitamin B complex.[9] However, prior to the discovery of vitamin B_{12} none of its recognized components alone or in combination was found to acquire increased hematopoietic power when simultaneously administered with gastric juice.[8] Pteroylglutamic (folic) acid [10] and its conjugates [11, 12] likewise have not been shown to be active as extrinsic factor in the sense of the above definition. On the other hand, vitamin B_{12} [4, 13] and its congeners, B_{12a} [14] and B_{12b} [15] (the last two probably synonymous), all acquire increased hematopoietic power when simultaneously administered with gastric juice.

A suitably prepared 70 per cent alcohol soluble extract of beef muscle is a convenient source of extrinsic factor, contains vitamin B_{12} upon microbial analysis and can be given either orally or parenterally. When such an extract is administered by parenteral injection its hematopoietic activity apparently depends entirely upon the vitamin B_{12} content.[10, 16] When administered orally, its potentiation by normal human gastric juice is no greater than when an equivalent amount of pure vitamin B_{12} is similarly employed.[16] Thus, it appears that vitamin B_{12} or closely related compounds in the food constitute the so-called extrinsic factor.

The hematopoietic effect of beef muscle extract [4, 10] and of vitamin B_{12} [13] upon parenteral administration *without* gastric juice is invariably greater than when these substances are given orally in identical amounts with gastric

juice. Therefore, the most economical use of the available facts permits the hypothesis that the function of normal human gastric juice in causing increased hematopoietic effects with beef muscle extract or with vitamin B_{12} is not to produce some new substance but merely to facilitate the absorption of vitamin B_{12} from the alimentary tract. This conclusion is supported by the recent demonstration [17] of the ability of one microgram of pure vitamin B_{12} to cause local maturation of megaloblasts when injected into the bone marrow cavity of a patient with pernicious anemia. This observation, which confirms the effect of purified liver extracts in vitro upon the uptake of radio iron by bone marrow cultures from patients with pernicious anemia,[18] renders improbable the existence of essential chemical modifications of the vitamin molecule in the food in the course of its absorption from the alimentary tract, or during its passage through or storage by the liver or other tissues while en route to the bone marrow. Thus it is likely that, except perhaps for loose combination or association with different proteins in its natural sources,[19] the so-called food (extrinsic) factor is identical with the antipernicious principle of liver and, in turn, with vitamin B_{12}.

In contrast to this gratifying progress is the present relative lack of new information concerning the nature of the so-called intrinsic factor of normal human gastric juice. This thermolabile, alkali-resistant, nondialyzable substance is present in normal human gastric juice in sufficient concentration to permit 10 c.c. of fresh gastric juice significantly to potentiate the hematopoietic activity of 5 micrograms of vitamin B_{12}.[19] Demonstrable activity persists when gastric juice is either passed through a Berkefeld filter [4] or is lyophilized and subsequently reconstituted.[20] The hog stomach, except for the pepsin secreting fundic portion,[21, 22] and the hog duodenum [21, 23] both contain a similar thermolabile constituent as well as a thermostable component which, like vitamin B_{12}, can be potentiated by simultaneous oral administration with gastric juice.[6] The normal human stomach, which is anatomically quite different from that of the hog, contains intrinsic factor in all its portions, though perhaps in lower concentration in the pyloric region.[22] Intrinsic factor is thus apparently secreted by those portions of the human stomach that are found to be degenerated in the disease pernicious anemia. Whereas duodenal secretions devoid of gastric juice are not a source of intrinsic factor in man,[24] human duodenal mucosa possesses such activity,[25] but perhaps only by passive absorption from contact with gastric juice.

Although extensive resections of the stomach and other portions of the alimentary tract in animals [26] have not led to the development of macrocytic anemia, the concentration of the antipernicious anemia principle in the liver is reduced by gastrectomy or by the production of an extensive gastric pouch with external fistula in the hog.[27] Review of the late effects of *total* gastrectomy in man indicates a high incidence of macrocytic anemia in patients surviving the operation for three or more years.[28] In "idiopathic" pernicious anemia, achlorhydria frequently long precedes the development of

the anemia, and there is often a striking familial incidence of achlorhydria, of early graying of the hair, and of the disease.[29] Nutritional deficiency may have a deleterious influence upon gastric secretion in experimental animals,[30, 31] and statistical studies demonstrate a greater incidence of achlorhydria in persons living on diets deficient in meat, green vegetables and fruit than in persons using these foods liberally.[32] Anacidity is said frequently to precede the development of pellagra,[33] and a deficiency of nicotinic acid-containing coenzyme has perhaps been experimentally implicated as its cause.[34]

It has been assumed that the intrinsic factor is an enzyme, though it is demonstrably not pepsin, rennin or lipase of gastric origin. Nevertheless, normal human gastric juice, after destruction of pepsin by exposure to alkali at pH 10 for 30 minutes, is effective as intrinsic factor and exhibits proteolytic activity against casein at pH 7.4.[35] Bonsdorff [36] has shown that this proteolysis is inhibited in vitro by extracts of the fish tape worm. In vivo as well, the worm appears to suppress the activity of constitutionally reduced amounts of intrinsic factor and so to precipitate the development of pernicious anemia in a few of the many persons in Finland harboring the parasite. The intrinsic factor has also been claimed to be a prolinase.[37] Fractions of hog stomach mucosa possessing concentrated alpha-aminopolypeptidase activity, when administered with derivatives of beef muscle, have been stated to exhibit hematopoietic power in pernicious anemia. Consequently it has been suggested that the intrinsic factor is an aminopolypeptidase.[38] However, subsequent observations [20] have failed to demonstrate intrinsic factor activity with aminopolypeptidase containing fractions derived from calf thymus; and normal human gastric juice has been found not to contain significant enzyme activity of this nature.

The most recent suggestion as to the nature of the intrinsic factor is derived from studies demonstrating that normal human gastric juice and fractions of hog stomach mucosa possess ability to render vitamin B_{12} unavailable for microbial growth.[39] This property has been presumed to explain the effectiveness of intrinsic factor in enhancing the hematopoietic activity of vitamin B_{12} upon oral administration by protecting it from destruction by the intestinal flora of the patient with pernicious anemia. However, to date no direct clinical demonstration of this function has been made, although it is of interest that the antibiotic aureomycin apparently increases the activity of orally administered vitamin B_{12} in pernicious anemia.[40] Nevertheless, fractions of hog stomach possessing strong binding capacity for vitamin B_{12} have been shown to be ineffective as sources of intrinsic factor when administered to patients with pernicious anemia.[4]

Relation of Folic Acid Deficiency to Nutritional Macrocytic Anemias

Let us now turn to the remarkable results of recent explorations concerning the nutritional requirements of microbes and of experimental ani-

mals. These together have made it clear that pernicious and related macrocytic anemias, far from being unique diseases affecting only man, are in fact manifestations of disturbances of metabolic processes fundamental to the biology of cells. The first steps on this important pathway were taken by Wills, who in 1935 produced in monkeys, by dietary means, a macrocytic anemia with megaloblastic bone marrow. As the anemia was shown in subsequent experiments not to respond to purified liver extract,[41] it was not until 1943 that a road-junction between this and other apparently unrelated investigations appeared as a result of the isolation of the so-called *L. casei* factor from liver independently by Pfiffner [42] and by Stokstad.[43] This substance, shortly thereafter synthesized in the form of pteroylglutamic acid,[1] was so named because of the discovery that it is required for growth by the *L. casei* organism. It was also found to prevent and to cure the nutritional macrocytic anemia of monkeys and of chicks, as well as to abolish the anemia and neutropenia of rats fed sulfonamides.[1] The last effect presumably depends upon the competitive action of the sulfonamide molecule upon the central para-aminobenzoic acid portion of the pteroylglutamic acid molecule, either in the metabolism of intestinal bacteria synthesizing the latter or in the tissues of the rat.

In 1945, shortly after pteroylglutamic acid was made available in synthetic form to the medical profession, Spies and his associates [44] reported striking hematopoietic and clinical effects in pernicious and other nutritional macrocytic anemias which were confirmed by numerous other workers. It has now become clearly established that pteroylglutamic acid in daily oral doses of one or more milligrams produces prompt increases in blood formation and at least initial clinical improvement in all varieties of nutritional macrocytic anemia, including pernicious anemia, sprue, tropical macrocytic anemia and the pernicious anemia of pregnancy and of tape worm infestation. It is highly effective in many cases of tropical macrocytic anemia [45] and of pernicious anemia of pregnancy,[46, 47] or of so-called megaloblastic anemia [48] as observed in the temperate zone in which purified liver extracts or vitamin B_{12} in usual dosage fail to be effective.[49] Similar failure to respond to vitamin B_{12} is noted [50] in some infants with nutritional megaloblastic anemia, but improvement is invariable with pteroylglutamic acid therapy. From the work of Luhby,[50] Zuelzer,[51] May [52] and their respective associates, this condition appears to be due to a deficiency of pteroylglutamic acid or of its closely related and metabolically active form, the so-called citrovorum factor. Both clinical and experimental work in monkeys indicates that the anemia is induced by a dominant deficiency of ascorbic acid in unsupplemented feedings with certain dried milk products containing the small amounts of pteroylglutamic acid present in the natural substance.

Folic acid was the name originally given to a factor extracted from spinach and essential for the growth of *S. lactis R.* Now sometimes applied collectively to pteroylglutamic acid and related compounds, it is also popularly used as a synonym for pteroylglutamic acid itself. In foods such as

leafy vegetables, liver or yeast, folic acid exists not as pteroylglutamic acid containing one molecule of glutamic acid joined to a pteridine through a para-aminobenzoic acid molecule, but chiefly in the form of conjugates. These contain additional linked molecules of glutamic acid to form a chain of three or seven.[1, 5] These conjugates, though active for the chick, monkey or rat, are not necessarily effective in promoting the growth of microorganisms until after treatment with "conjugases" present in animal tissues that remove the extra glutamic acids. The triglutamate is as active as pteroylglutamic acid in promoting the growth of *L. casei*, but much less so for *S. lactis R.* The heptaglutamate isolated from yeast is unable to stimulate the growth of either organism until converted to the monoglutamate form. The situation is further complicated by the presence in foods of "inhibitors" of the conjugases.[12] However, the inhibitors do not seem to be of clinical importance in this particular way because the pure triglutamate is apparently as active upon oral or parenteral administration in some cases of pernicious anemia as is an equivalent amount of the monoglutamate.[16, 53, 54] The results of the few observations made with the pure heptaglutamate are conflicting. However, in certain patients with pernicious anemia or sprue it has been found to be active hematopoietically, and its parenteral administration has led to a rapid excretion of free folic acid in the urine [16] that was perhaps sometimes increased by the simultaneous injection of liver extract. At least in vitro normal human gastric juice has no conjugase activity,[11] although it is conceivable that it may possess anti-inhibitor power.[12]

Although pteroylglutamic acid was naturally at first thought to be the antipernicious anemia principle, it was soon recognized [1, 46] that this substance was virtually lacking in purified extracts of liver highly effective in initiating and maintaining improvement in all aspects of pernicious anemia. Subsequently it developed that treatment of patients with pernicious anemia *exclusively* with pteroylglutamic acid often failed to produce a complete hematologic remission or to maintain it when once achieved.[55, 56] Glossitis sometimes reappeared, and a considerable incidence or progression of subacute combined degeneration of the spinal cord developed. This was especially common when large daily doses of pteroylglutamic acid were given in efforts to maintain normal blood values. It has been suggested that either pteroylglutamic acid competitively inhibits the metabolism of glutamic acid by the nervous system,[55] or that it forces a biochemical reaction requiring vitamin B_{12} [56] and so induces a deficiency of vitamin B_{12} or of the metabolic processes dependent upon it. At any rate, the substitution of purified liver extract or vitamin B_{12} for pteroylglutamic acid therapy produces a prompt and complete hematologic and clinical remission which is maintained as long as such therapy is continued.[56] Moreover, preliminary evidence [57] indicates that daily therapy even with large amounts of pteroylglutamic acid presents no hazard to the nervous system provided the amounts of purified liver extract or of vitamin B_{12} usually employed in the treatment of pernicious anemia are injected at monthly intervals.

Animal experiments [2, 58, 59] and the incomplete responses in pernicious anemia to pteroylglutamic acid [55, 56] indicate that both vitamin B_{12} and pteroylglutamic acid are required for normal hematopoiesis, and perhaps also for the functional integrity of the gastrointestinal tract and of the nervous system in man. As in bacteria,[1, 2, 3] the action of these substances may be through effects upon the formation of nucleic acids and nucleoproteins by means of chemical reactions arranged in parallel or in series. Richard Vilter and his associates [56] have shown the effectiveness of uracil in doses of 15 to 30 gm. daily in pernicious anemia. In patients who relapsed while being maintained upon pteroylglutamic acid, they found that thymine (methyl uracil) can complete a partial remission induced by choline and methionine administration. Thus, apparently certain pyrimidines may be hematopoietically active in nutritional macrocytic anemias and so indicate that in these conditions deficiencies of pteroylglutamic acid or of vitamin B_{12} lead to a maturation arrest in the metabolism of the nucleoproteins of the erythroid cells of the bone marrow.

Very recently a compound closely related chemically to pteroylglutamic acid has been discovered. In fact, it is perhaps its biologically active form in certain bacteria and in animals.[60] This, the so-called citrovorum factor, was discovered by Sauberlich and Baumann.[61] Like folic acid, it is present in crude liver and yeast extracts but is virtually lacking in some purified extracts of liver. It is presumably successfully synthesized from the components of the basal medium by *L. casei* but not by *Leuconostoc citrovorum*. The latter apparently requires it as a preformed molecule and hence serves as a convenient test organism. Citrovorum factor has been synthesized by hydrogenation of formyl folic acid. It is evolved from folic acid by rat liver slices, a process that is accelerated by the presence of ascorbic acid.[62]

Citrovorum factor appears to be about as active hematopoietically in pernicious anemia as is pteroylglutamic acid.[63] When pteroylglutamic acid is fed to normal subjects, citrovorum factor is excreted in the urine. In patients with scurvy, however, such excretion is small until after vitamin C is administered.[64] Aminopterin in appropriate amounts inhibits the growth-promoting activity of folic acid in microörganisms, mice and chick embryos. Citrovorum factor, on the other hand, provides active competition with the action of aminopterin under these conditions, as well as with its action in controlling mouse leukemia.[65] In pernicious anemia, aminopterin in appropriate amounts prevents the hematopoietic effect of folic acid but not of citrovorum factor [63] or of vitamin B_{12}.[66]

Vitamin B_{12} as the Anti-Pernicious Anemia Principle

At last, in 1948, after 20 years of endeavor, the nature of the antipernicious anemia principle was disclosed with the isolation of vitamin B_{12}.[67] The pure vitamin, originally prepared from liver, has been shown to initiate [68] and to maintain complete hematologic and clinical remission [3, 56, 69] in nearly

all cases of Addisonian pernicious anemia, quite as do highly purified extracts of liver. Because such effects can be produced by the daily injection of as little as one microgram of the pure vitamin, it is apparently one of the most active pharmacologic agents known. However, presumably because of the lack of the so-called gastric (intrinsic) factor, in most patients with pernicious anemia the daily oral administration of as much as 50 micrograms of vitamin B_{12} is relatively ineffectual.[70] This ratio between parenteral and oral dosage resembles that previously observed with liver extracts. The ready availability of injectable preparations of pure or of concentrated vitamin B_{12} from microbial sources promises to permit their elective substitution for the present successful use of purified extracts of liver. Presumably vitamin B_{12} also need be injected for maintenance purposes no more often than once a month.

It is indicative of the high level of scientific achievement of the laboratories of the leading members of the pharmaceutical industry that, as with the isolation and identification of pteroylglutamic acid, theirs is also the credit for the discovery of vitamin B_{12}. Guided by the deep pink band in partition chromatography of refined liver extracts, concentrated preparations were achieved by Lester Smith[71] in England in 1948 and were shown by Ungley to be highly active clinically. Shortly thereafter, in the United States, Folkers and his associates[67] achieved the isolation of a red crystalline material which was shown by the late Dr. Randolph West[68] to have striking hematopoietic activity in pernicious anemia. The American work was aided by the prior discovery of Shorb[72] that the growth of *L. lactis* (Dorner) in a basal medium was promoted by the addition of purified liver extracts roughly in proportion to their activity in the treatment of pernicious anemia.

This last observation, made in the course of a search for a microörganism requiring for growth the so-called "animal protein factor,"[2, 3] provided another road-junction with a pathway of progress in knowledge concerning a water soluble nonprotein factor closely associated with animal but not with most vegetable proteins. Previous workers had shown that this material was required in the diet of laying hens for satisfactory hatchability of eggs and for the early growth of chicks, and that it was necessary for the prevention of a high mortality in young rats born of mothers fed with rations containing proteins of plant origin. In addition to such sources as fish meal and purified liver extracts, uninhibited scientific curiosity had also discovered that cow manure, rumen contents and hen feces contained animal protein factor. This suggested that it was a product of microbial synthesis, and led to the demonstration that various microörganisms, including the *Streptomyces griseus* and a rodlike organism derived from hen feces, would produce animal protein factor active in chicks and in the treatment of pernicious anemia.[2, 3] Vitamin B_{12} has now become a byproduct of the microbial production of antibiotics, a process that will probably replace liver as a commercial source of vitamin B_{12}. The satisfactory state of the present treat-

ment of pernicious anemia fortunately permits us to enjoy without regret the recent paradoxic discovery by Bethell and his associates [47] that the feces of the patient with pernicious anemia contain a supply of vitamin B_{12} ample to prevent the disorder were it parenterally available to the patient.

Although the structural formula of vitamin B_{12} is not completely known, the molecule has fascinating properties, and one of its degradation products resembles somewhat the molecule of riboflavin.[3] Its molecular weight is of the order of 1,500. The red color is due to the presence of an atom of cobalt which is bound coördinatively to a cyano group.[73] An atom of phosphorus is also present, and nitrogen but no sulfur is found upon analysis. Hydrolysis does not release alpha amino acids and so excludes a polypeptide structure. No resemblance to the pterin-type arrangement of part of the molecule of pteroylglutamic acid has been noted. The second red component of purified liver extracts originally noted by the British workers in chromatographic columns has been found to be produced by microbial synthesis as well.[74] This, the form in which most of the vitamin appears in natural sources, has recently been designated as vitamin B_{12b} and is probably identical with vitamin B_{12a}.[75] It lacks the cyano group of vitamin B_{12} but can be converted to the latter in aqueous solution by the addition of cyanide ion.[75] Although the chemical and spectroscopic properties of these forms of vitamin B_{12} differ, their ability to promote microbial growth or hematopoietic activity in pernicious anemia is apparently similar.

The Hemolytic Process in Pernicious Anemia

Whipple [76] recognized in his classic studies that the greatly increased output of bile pigment by the severely anemic patient with pernicious anemia was in all probability not wholly derived from the destruction of circulating red cells. The maturation arrest theory of Peabody,[77] now firmly established by serial bone marrow punctures showing the rapid disappearance of the megaloblasts within the first two to three days following the injection of liver extract,[78] is also inconsistent with a greatly increased rate of red cell destruction. There is, however, incontrovertible evidence that the red cells of patients with pernicious anemia have a somewhat shortened life span. Thus, when transfused into normal subjects with compatible blood groups, pernicious anemia red cells do not survive normally [79] unless derived from patients who are in complete remission as the result of liver therapy.[80] However, because such studies by means of the differential agglutination technic of Ashby have demonstrated a normal survival span for normal red cells transfused into the patient with untreated pernicious anemia, it is not possible to attribute the rapid decrease in bile pigment output following the injection of liver extract [81] to a prompt cessation of destruction of the circulating red cells by humoral factors. Clearly, more time would be required for a reduction of the pigment output, were this due to replacement of the defective red cells by the increasing number of more durable new red cells in circulation.

London and his associates,[82] by feeding glycine labeled with N15 to a patient with pernicious anemia, have determined the chronology of its concentration and persistence in the blood stream after incorporation in the hemoglobin of the circulating red cells. Their studies indicate that the mean survival time of the red cells is about 72 as opposed to 120 days in the normal individual. Of greatest interest are their data concerning the source of the bile pigment in the stools, which indicate that 40 or more per cent of the labeled urobilin recovered was not derived from circulating red cells. Indeed, in normal subjects this is true to an extent of at least 10 per cent. In view of the established morphologic evidence for maturation arrest in the bone marrow, the origin of the excess bile pigment in the stools not accounted for by the destruction of circulating red cells would not seem likely to be red cells destroyed before leaving the bone marrow. The source might then be either porphyrins not used for the production of circulating hemoglobin or, as Whipple suggested, direct synthesis of bilirubin or other bile pigments—without porphyrin ring formation. The finding of excess coproporphyrin I in the stools [81] would favor the first of these alternatives. In any case, the results of the studies reviewed in this article allow the conclusion that in pernicious anemia, as a result of a conditioned deficiency of vitamin B_{12}, both the rate of formation and the quality of the red cells produced are subnormal.

Conclusions

The information presently available suggests that Addisonian pernicious anemia is the clinical result of a deficiency chiefly of vitamin B_{12}. This deficiency is predominantly due to a lack of gastric secretion, itself usually a manifestation of hereditary predisposition and of advancing age. In some patients, local disease or surgical ablation destroys this essential function of the stomach. The consequent failure of vitamin B_{12} to be assimilated adversely affects hematopoiesis and frequently also the integrity of the alimentary tract and of the nervous system. The proximal cause of the macrocytic anemia is both decreased production and increased destruction of defective red cells. Either both processes must be of only moderate degree, or the magnitude of each must be inversely related to that of the other.

Defective diets and intestinal dysfunction or disease, especially when gastric secretion is not significantly disturbed, may result in nutritional macrocytic anemia in which the predominant deficiency is not of vitamin B_{12} but of pteroylglutamic acid. Dietary deficiency of ascorbic acid probably restricts the formation of the metabolically active and closely related form of pteroylglutamic acid known as the citrovorum factor, or folinic acid. Vitamin B_{12}, pteroylglutamic acid and ascorbic acid are apparently required for normal hematopoiesis. The full significance of their interrelations with respect to the nucleoprotein metabolism of microbes, of animals and of man remains to be disclosed.

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TREATMENT OF ANGINA PECTORIS WITH PROPYLTHIOURACIL *

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TOTAL thyroidectomy in the treatment of angina pectoris, first performed in 1933 by Blumgart, Levine and Berlin,[1] was employed over a period of years until the lack of sufficiently favorable results led to virtual abandonment of the procedure. Not only was there a fairly serious operative risk but, if the patient's angina was not ameliorated, he was then left with an additional disorder, myxedema. Nevertheless, a review of the literature concerning total thyroidectomy in the treatment of angina indicates that some patients obtained considerable relief following operation. It must be remembered, of course, that the natural course of angina is often marked by remissions and exacerbations. Climatic conditions, situational and psychogenic factors, progressive narrowing of coronary arteries, all may significantly influence the severity of the anginal syndrome and yet be difficult to quantitate. Enthusiasm over a new form of treatment, enthusiastically prescribed, may be accompanied by an improvement ascribed to the therapy.

The introduction of antithyroid drugs afforded an opportunity to produce myxedema in patients with angina pectoris without a formidable operation or permanent loss of thyroid function. Raab [2] was the first to administer thiouracil to patients with angina. To 10 individuals with this syndrome he gave 400 to 600 mg. daily followed by a maintenance dose of 100 mg. daily. Treatment periods varied from one and one-half to three and one-half months. In four patients, symptoms disappeared during therapy; in three, they became less frequent and intense. Of the three failures, one died of coronary occlusion after one month of therapy. Improvement began within one and one-half to three weeks in four cases; within four to six weeks in three. After the drug was discontinued improvement was maintained for from two weeks to 11 months.

Ben-Asher [3] administered thiouracil, in similar dosage, to 37 patients with angina. Six were treated less than nine days, because of drug fever in five and fatal coronary occlusion in one. Results were considered excellent in seven, good in 13, fair in five and poor in 11. Improvement began within one to three weeks in 15; within four to six weeks in 10. After the drug was discontinued, improvement was maintained for from two to 16 months.

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DiPalma and MaGovern [4] were not enthusiastic about the results of treatment in eight patients with angina. In four, thiouracil was discontinued within three to eight weeks, because of drug rash in two, severe dyspnea in one, and failure to lower the basal metabolic rate in one. Four patients were treated for over a year. In only two was angina thought to be significantly improved. One was able to return to work for the first time in two years. The second was improved for a few months, but was suspected of masked hyperthyroidism because of a single pretherapy basal metabolic rate of plus 55.

In a careful study of nine patients, Frisk and Lindgren [5] noted marked and sustained improvement in eight, two of whom had previously been subjected to cervicothoracic ganglionectomy without lasting effect. Four hundred to 500 mg. methylthiouracil were administered daily, gradually reduced to a daily maintenance dose of 15 to 50 mg. In one patient, thiouracil was substituted because of drug fever on the ninth day of therapy with the methyl form. Treatment was continued for from 10 to 23 months. Improvement was first noted within one and one-half to five months after beginning therapy. Exercise tolerance tests were done in four and showed a fourfold to sevenfold increase in tolerance. Hypoxia tests were done in six, and showed increased tolerance in all. Improvement coincided with a drop of the basal metabolism in five. Mild myxedema occurred in four. However, marked lowering of the basal metabolic rate was not found essential in all cases for beneficial results.

The present report concerns seven cases of angina pectoris treated with propylthiouracil.

Materials and Methods

The patients fulfilled the following criteria:

1. Angina had been present for more than one year.
2. It had been produced regularly by the same or decreasing amounts of exertion for six months or longer.
3. There was no evidence of recent myocardial infarction or congestive failure.
4. The only apparent cause of the angina was coronary arteriosclerosis.
5. During a hospital observation period of four weeks or more before therapy was commenced, there were no significant changes in the severity of angina.

During the control observation period and throughout the period of propylthiouracil administration, frequent observations were made of the basal metabolic rate, exercise tolerance, blood pressure, pulse rate and body weight. Total and differential leukocyte counts were performed thrice weekly during the early months of therapy, and then at longer intervals. Serum cholesterol was determined by the Sperry-Schoenheimer method.[6]

Protein-bound serum iodine was determined by Dr. Douglas Riggs, of the Harvard Medical School, employing the method described by him.[7]

The exercise tolerance test was always performed in the same room. For three hours after lunch the patient rested, without smoking. Ice was held in both hands for two minutes before beginning and throughout the test. One ascent and one descent of a two-step staircase [8] were counted as a single trip. The trips were made at a regular pace determined by each patient, and the time interval recorded. The test was terminated upon the onset of angina, marked fatigue or dyspnea. Although the room temperature varied, this factor was not considered significant in evaluating exercise capacity, since similar temperatures occurred often enough during the course of observation to permit comparison of the exercise tolerance at various stages of therapy at nearly identical temperatures.

Smoking was not restricted, sedation was not given, and nitroglycerin was used freely as needed. Throughout hospitalization, the patients' activities were limited only by their own capacities. Because of the extensive area encompassed by the hospital and its many occupational and recreational diversions, the patients had free range of movement, and spent time on their wards only as they desired. They recorded their number of anginal attacks daily. Propylthiouracil was usually given at intervals of six hours. After the basal metabolic rate began to drop, the midnight dose was shifted to 10 p.m. A standard initial and maintenance dose was not established.

Case Reports

Case 1 (chart 1). A 57 year old man entered the hospital on December 31, 1946. He had stopped work in 1945 because of brief episodes of unconsciousness during the past five years. Two years before entry he had begun to have substernal pain on exertion and excitement, relieved by rest and nitroglycerin. One year before entry he had had severe anterior chest pain lasting three hours, following which he had been kept in bed for three weeks. For eight months before entry, angina was more easily precipitated, and appeared under constant conditions. Emotional disturbances, climbing one flight of stairs at a normal pace, walking a few blocks on level ground, or a lesser distance in cold or wet weather, regularly produced pain. Its frequency varied from several times daily to once weekly, depending on the degree of activity and emotional stress. During this same period, activity had also been limited by intermittent claudication in the right leg on walking.

Physical Examination: Blood pressure 170 mm. Hg systolic and 110 mm. diastolic; pulse 70. The eyes were not prominent and the ocular fundi were normal. The thyroid was not felt. Pressure on the carotid sinuses caused slight slowing of the heart but no symptoms. The heart was normal in size, sounds were of good quality, there were no murmurs, and the rhythm was regular. The lungs were clear. The hands were warm, dry and without tremor. Arterial pulsations were absent in both feet.

Laboratory Data: Examination of the blood, urine and spinal fluid was normal. Kahn test was negative. Wintrobe sedimentation rate was 12 mm. per hour. Roentgenograms of skull, chest and legs were normal. Electroencephalogram showed abnormal, generalized fast paroxysmal rhythm. Electrocardiogram was within normal limits at rest. After exercise, with production of angina, there was marked de-

pression of ST in limb leads and CF_4 totaling 4.5 mm. T_1 and T_2 became diphasic. Frequent electrocardiograms at rest were normal throughout the course.

Course: One week after entry the blood pressure had fallen to 130 mm. Hg systolic and 80 mm. diastolic. On frequent recordings thereafter it always remained within normal limits. The pulse rate was 60 to 70 throughout the course.

For six weeks the patient was observed without treatment. There was occasional substernal pain on moderate exertion. Basal metabolic determinations during this period varied from plus 17 to plus 23. There were no clinical features to suggest hyperthyroidism. Maximum exercise tolerance test was 58 trips.

On February 14, the administration of 200 mg. propylthiouracil every six hours was commenced. After nine weeks of therapy the basal metabolic rate dropped to plus 1, and exercise tolerance rose to 72 trips, being terminated by pain in the right

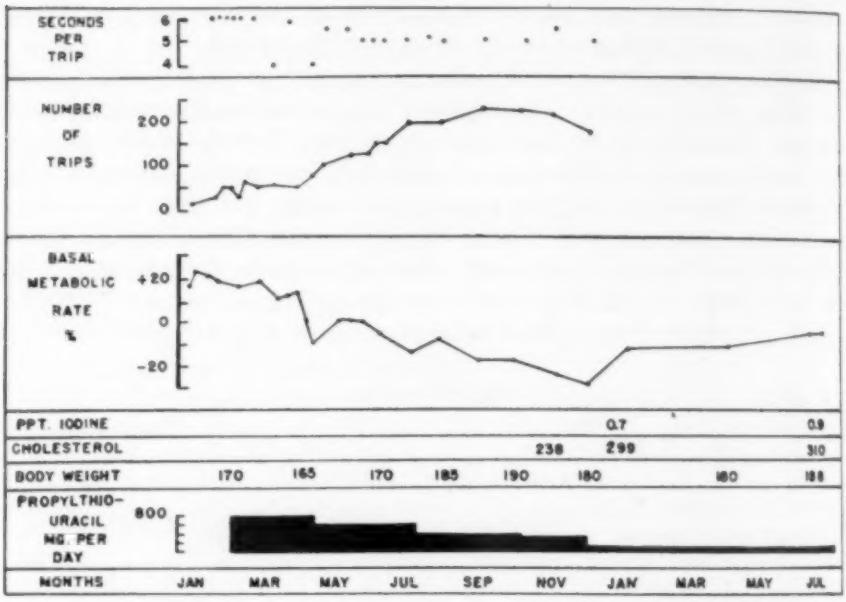

CHART 1. Case 1.

Ppt. iodine = serum protein-bound iodine in micrograms per 100 c.c. Serum cholesterol, mg. per 100 c.c. Body weight, pounds.

leg. There was no chest pain. During the next two months exercise tolerance increased, and was limited only by leg pain.

Coincident with the performance of Buerger's exercises, leg pain decreased and finally disappeared. After 20 weeks he completed 200 trips without pain, stopping because of fatigue. His basal metabolic rate at this time was minus 15, and he showed slight puffiness of eyelids and face, together with a little enlargement of the thyroid gland.

After discharge in July, 1947, he was seen at monthly intervals. Propylthiouracil was gradually reduced to 50 mg. every eight hours. In December, the tolerance test was limited by pain in the right knee, which was the seat of osteoarthritic changes. After this, satisfactory exercise tolerance tests could not be done because pain developed in the knee after 50 trips.

Throughout the period of treatment, he had no angina except for three brief episodes on exertion in January, 1948. Activity was unrestricted. This included brisk walking for three to four miles in all kinds of weather, running one and a half blocks for a bus, climbing two flights of stairs quickly, rowing a boat with some vigor, and changing automobile tires.

In August, 1948, the patient was reported to have drowned while fishing.

Summary: Angina had been present for two years before administration of propylthiouracil. After nine weeks of therapy, coincident with a decline in the basal metabolic rate, exercise tolerance increased markedly. Very mild clinical myxedema developed. There was freedom of activity for 15 months; and almost complete absence of angina.

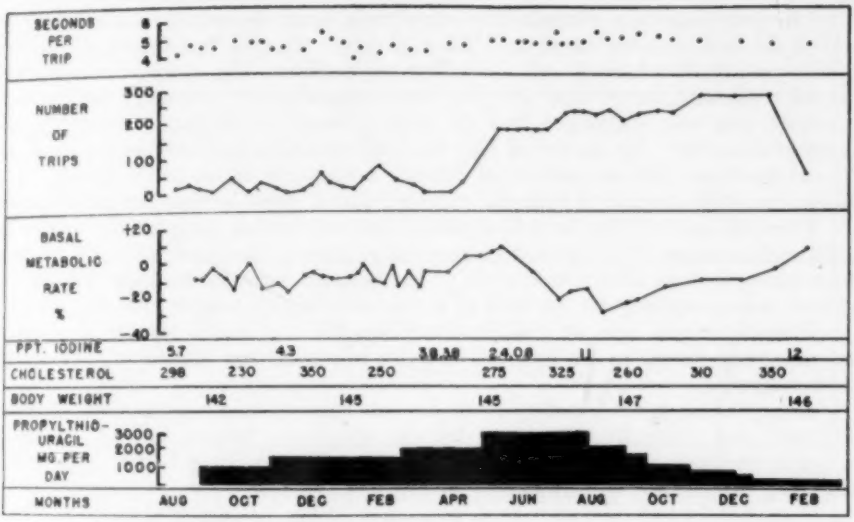

CHART 2. Case 2.

Case 2 (chart 2). A 56 year old man entered the hospital on August 6, 1947. Seven years before entry he had occasionally experienced heavy, upper substernal pressure on walking fast or climbing several flights of stairs. It was of short duration and disappeared with rest. One year before entry there was marked midsternal pain, lasting three-quarters of an hour and accompanied by sweating. Following this episode angina occurred one to 10 times daily, at work, on walking slowly on level ground for 10 minutes, and rarely at bed rest. He stopped work in June, 1947.

Physical Examination: Blood pressure 112 mm. Hg systolic and 84 mm. diastolic; pulse 76. There was a small nodule, 1.5 cm. in diameter, in the thyroid isthmus. The heart was normal in size, sounds were of good quality, there were no murmurs, and the rhythm was regular. The lungs were clear.

Laboratory Data: Examination of the blood was normal. Urine was normal except for 1 plus sugar. Kahn was negative. Wintrobe sedimentation rate was 4 mm. per hour. Glucose tolerance test: fasting blood sugar 100 mg. per 100 c.c.; at one-half hour 178 mg.; at one hour 178 mg.; two hours 182 mg.; three hours 130 mg. Serum cholesterol was 298 mg. per 100 c.c. Roentgenograms: chest normal; legs showed minimal arterial calcification. Repeated electrocardiograms, throughout the

course, were within normal limits at rest and showed no change after the production of angina by exercise.

Course: For one month the patient was observed without treatment. Basal metabolic rate was minus 11. Maximum exercise tolerance test was 24 trips.

On September 8, the administration of 250 mg. propylthiouracil every six hours was begun. During the next five months it was gradually increased to 500 mg. every six hours. By January the thyroid was moderately enlarged. In April the basal metabolic rate and exercise tolerance showed no change, and angina still occurred several times a day after two to five minutes of slow walking, and more quickly after a meal. At this time, direct hourly measurements of radioactivity over the thyroid gland, after administration of a tracer dose of radioactive iodine,* indicated that propylthiouracil blocked to some extent the collection of iodine in the thyroid. However, since 27.4 per cent of the dose was collected in the gland 48 hours afterwards, it was concluded that the blocking effect of propylthiouracil was small.

The drug was then administered every three hours (except at 3 a.m.), and on May 3 the dose was increased to 3,000 mg. daily. During this month the thyroid became very much enlarged, and a bruit became audible. The exercise tolerance test showed a marked rise on May 20 (200 trips without pain). At this time the basal metabolic rate was unchanged, but the protein-bound iodine had dropped into the hypothyroid range. By the end of July the basal metabolic rate had dropped to minus 24, and there was definite puffiness of the face with slight edema of the eyelids. The patient had mild discomfort from the enlarged gland, some lacrimation and lassitude.

From the end of May he was almost completely free of angina. By August he could walk twice as fast as he had six months previously, and could maintain his pace three-quarters of an hour. While out of the hospital for a fortnight he was able to be very active, walking for an hour at a time over rocky beaches without pain.

Propylthiouracil was gradually reduced to 250 mg. every six hours. During the remaining period in the hospital, exercise tolerance was maintained and angina did not recur.

After discharge in October, 1948, he was seen at monthly intervals. Propylthiouracil was gradually reduced to 100 mg. every six hours. During November, he began to have occasional episodes of angina when walking into a heavy wind, ascending three flights of stairs quite rapidly, and climbing a long steep grade. During December, he had pain after brisk walking outdoors for five to 15 minutes, but his exercise tolerance test remained unchanged. During January, angina occurred after walking five minutes. The exercise tolerance test dropped to 65 trips and was terminated by pain.

There was no change in his myxedematous appearance.

Summary: Angina had been present for seven years before administration of propylthiouracil. Not until 3,000 mg. were given daily, in divided doses at three hour intervals, did there appear to be marked evidence of antithyroid action. Coincident with a drop of the protein-bound iodine into the hypothyroid range, the exercise tolerance increased markedly. This occurred before there was a decline in the basal metabolic rate. Moderate myxedema developed. There was almost complete absence of angina for six months. It then recurred on mild activity, and the exercise tolerance decreased considerably despite continued myxedema.

Case 3 (chart 3). A 57 year old man entered the hospital in January, 1947. Eighteen months before entry he had begun to have lower substernal tightness

* By Dr. Bengt Skanse, of the Massachusetts General Hospital.

radiating to the precordium and left upper arm when he worked, quickly relieved by rest. While walking three-quarters of a mile to and from his job, he would have to stop several times because of recurrent pain. During the next year, work tolerance steadily declined. Pain occurred at rest and under slight emotional stress. For six months before entry his activity tolerance was fairly constant. He was usually unable to walk 100 yards on the level and could not climb more than 12 steps without pain. Five months before entry he stopped work and rested at home for 10 weeks, without improvement. He returned to his job but had to give up after 10 days. The next five weeks were spent at complete bed-rest, but there were short episodes of angina precipitated by excitement, speaking at any length, or turning about quickly in bed.

Physical Examination: Blood pressure 140 mm. Hg systolic and 86 mm. diastolic; pulse 80. The heart was normal in size, sounds were of good quality, there were

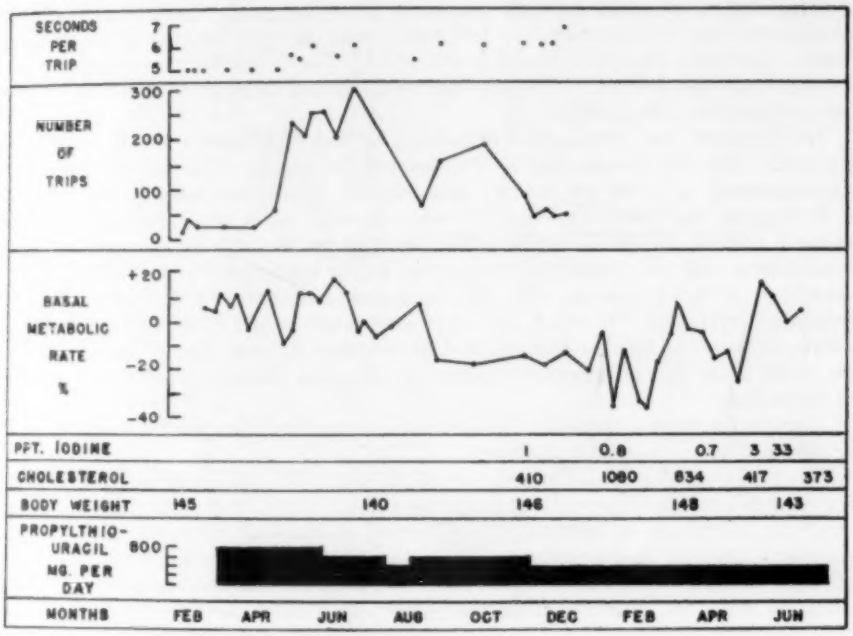

CHART 3. Case 3.

soft systolic murmurs at the mitral and aortic areas, and the rhythm was regular. The lung fields were clear.

Laboratory Data: Examination of the blood and urine was normal. Kahn test was negative. Wintrobe sedimentation rate, repeated frequently throughout the course, was 22 to 28 mm. per hour. Electrocardiograms were identical during the first year of observation and therapy and showed evidence of myocardial damage.

Course: For two months the patient was observed without treatment. At rest or on very limited effort he had two to four attacks of angina daily, relieved by nitroglycerin. Basal metabolic rate was plus 3. Maximum exercise tolerance test was 25 trips.

Two months after entry, administration of 200 mg. propylthiouracil every six hours was commenced. During the first month of therapy his exercise tolerance did

not change. However, spontaneous anginal attacks decreased after three weeks and disappeared after one month. At seven weeks he had to stop after 60 trips because of dyspnea. Pain did not occur. At eight weeks he completed 228 trips painlessly. His basal metabolic rate was minus 11. At 10 weeks his appearance was mildly myxedematous, with coarsening of features, puffiness of eyelids, some dulling of personality, and slight thyroid enlargement. The patient's myxedematous appearance at this time cast doubt on the validity of the basal metabolism values obtained during May and June. At 14 weeks, he completed 300 trips without pain. By this time, his activity had increased to include a two-mile walk, one to three times daily, done in 30 to 45 minutes.

After discharge in July, 1947, he was seen at monthly intervals. His routine included a one and a half mile walk at a normal pace four times daily. In August he complained of precordial distress after 66 trips. In September he completed 150 trips, stopping because of marked fatigue. In October he had chest pain briefly on six occasions, on two cold days, after walking 50 to 100 yards against the wind. At this time he was able to complete 180 trips, stopping only because of marked leg fatigue. His basal metabolic rate was minus 22. There had been no increase in his myxedematous appearance. His daily routine continued to include a one and one-half mile walk several times daily.

In November, on six separate occasions, he had pain after walking one-quarter of a mile. He was re-admitted to the hospital for study. His thyroid gland now was moderately enlarged and a bruit was present. Forty-two trips on the step test led to angina, and there was mild distress on walking a short distance outdoors against a cold wind. In December, after 46 trips on the step test, he suddenly lost consciousness and for a minute or two there was a cessation of respiration and disappearance of heart sounds. The electrocardiogram at this time suggested acute myocardial infarction. However, one-half hour later it had returned to its original pattern. The white blood cell count and temperature did not rise. The episode was considered to be due to myocardial ischemia. Further exercise tolerance tests were not attempted.

During the ensuing months there was discomfort once or twice weekly on walking outdoors or fairly rapidly indoors.

Beginning on April 13, he was given thyroid gr. 0.5 daily, to determine the effect of raising his metabolism while maintaining him on propylthiouracil. After 18 days there was no change in his appearance, serum iodine (0.7 microgram) or activity tolerance. On May 1, thyroid gr. 1 daily was begun. During the next 10 days he had eight attacks of angina on mild effort, and once he was awakened by chest pain lasting 30 minutes. Electrocardiogram showed no change, and the white blood cell count and temperature did not rise. At this time his protein-bound iodine was 3 micrograms, his appearance was much less myxedematous, and the thyroid was slightly smaller. On May 28, thyroid was increased to gr. 1.5 daily. After one month on this dosage, his face had lost all evidence of myxedema and the thyroid was barely palpable. His serum cholesterol had dropped from 834 to 417 mg. per 100 c.c., the basal metabolic rate varied from plus 5 to minus 5, and the protein-bound iodine was 3.3 micrograms. He had to walk more slowly to avoid chest pain, especially after meals, and there were occasional nocturnal anginal episodes. On July 14, he experienced prolonged chest pain, developed shock, and died 24 hours later.

Summary: Increasingly disabling angina had been present for 18 months before administration of propylthiouracil. After eight weeks of therapy, coincident with a decline in the metabolic rate, exercise tolerance increased markedly. Moderate myxedema developed. There was almost complete freedom from angina with increased activity tolerance for a year, although

there was a marked decline in this tolerance after six months. With administration of desiccated thyroid in dosage sufficient to raise protein-bound iodine to slightly subnormal level and to cause disappearance of clinical myxedema, activity tolerance was reduced, with increase in frequency and severity of angina, and termination in a fatal attack.

Case 4 (*chart 4*). A 58 year old man, unemployed for three years, entered the hospital in June, 1947, for the fifth time in eight months because of severe angina pectoris. At no time had there been clinical evidence of myocardial infarction.

For three years he had had substernal pressure radiating to both arms on exertion or excitement. Nitroglycerin was used daily with relief. His activity had been limited to driving his wife to and from the railroad station, cooking supper, and walking about his yard. There was pain on shaving, climbing four steps and walking

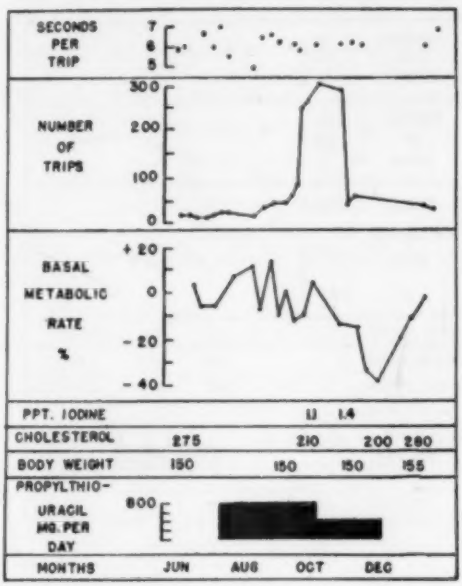

CHART 4. Case 4.

25 feet uphill, but none when walking slowly on the level. For one year he had occasionally been awakened by pain.

Physical Examination: Blood pressure 120 mm. Hg systolic and 80 mm. diastolic; pulse 80. The heart was normal in size, sounds were of good quality, there were no murmurs, rhythm was regular. The lungs were clear.

Laboratory Data: Examination of the blood and urine was normal. Kahn test was negative. Wintrobe sedimentation rate was 14 mm. per hour. Roentgenogram of the chest was normal. Electrocardiogram was normal.

Course: For five weeks he was observed without treatment. He had 24 attacks of pain during this time, 17 at rest and seven on effort. The basal metabolic rate was minus 7. Maximum exercise tolerance test was 14 trips.

On July 21, the administration of propylthiouracil, 200 mg. every six hours, was commenced. The optimism evoked by this new form of therapy was believed to be responsible for the decrease of attacks at rest in the next 10 days (two at rest, four

on effort). There were no further attacks until September 4, when he had substernal pain after pushing a patient up-grade in a wheelchair. Between the sixth and eighth weeks of therapy, exercise tolerance rose steadily. The basal metabolic rate at this time was minus 13. At 10 weeks, he completed 300 trips without pain. He was able to climb three flights of stairs painlessly, something he had not been able to do for two years. At the end of 12 weeks his protein-bound iodine was 1.1 micrograms, and his basal metabolic rate was minus 17. He had moderate puffiness of the face, edema of the eyelids, sleepiness and lassitude.

He was discharged on October 15 and had no angina for the next month. His activities included walking three miles in 70 minutes, climbing stairs, and ascending 15 per cent slopes for 200 yards.

On November 12, while at rest, he had intermittent midsternal pressure and pain through the left arm, lasting two to three hours at a time and persisting for 12 hours. On the next day, his basal metabolic rate (minus 19) and blood iodine level (1.4)

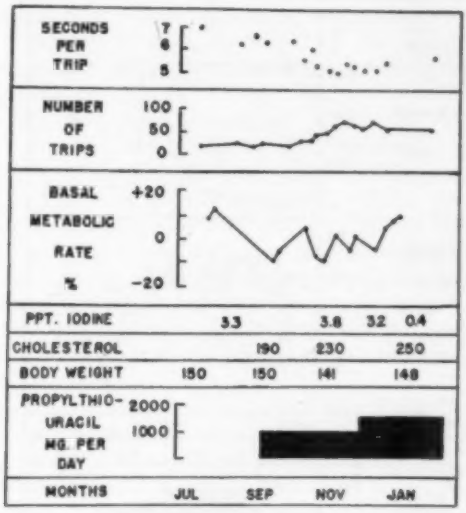

CHART 5. Case 5.

were practically identical with those of October 19 (minus 17 and 1.1). Electrocardiogram was normal and showed no change after his exercise tolerance test which, however, was terminated by pain at 38 trips. A few days later, his tolerance was 50 trips, terminated by pain. Frequent prolonged attacks of chest pain, most of them at rest, then occurred almost daily, even though the basal metabolic rate dropped to minus 40, with further increase in his myxedematous appearance.

On December 12, propylthiouracil was discontinued. Evidence of myxedema disappeared within a month, without significant change in frequency or severity of chest pains. Electrocardiograms during this period showed very transient changes consistent with myocardial ischemia. On February 4, a dorsal sympathectomy was performed. Following this he felt much improved, being moderately active but with occasional tightness in the chest.

Summary: Angina had been present for three years before administration of propylthiouracil. After eight weeks of therapy there was a sharp increase in exercise tolerance, at which time the basal metabolic rate was essentially

unchanged. Clinical myxedema was apparent at 12 weeks. After 15 weeks, despite continued myxedema, his exercise tolerance fell abruptly. It was not affected by further decline in the basal metabolism, nor by cessation of propylthiouracil and return of the basal metabolism to normal.

Case 5 (*chart 5*). A 51 year old man was admitted on June 1, 1947, for renal colic and hematuria. Symptoms of coronary insufficiency had been present for nine years, and he had not worked for eight and one-half years. He had been hospitalized five times for severe attacks of chest pain, the last time in October, 1946. Since then he had had dyspnea on mild exertion and had been taking digitalis. Throughout these years, there was squeezing substernal pain almost daily, precipitated constantly by walking on level ground at an ordinary pace for 40 feet, climbing a flight of stairs, and by excitement, but relieved by nitroglycerin. He could walk a mile on level terrain very slowly. For three years he had had occasional severe chest pain lasting several hours, relieved by hypodermic injections.

Physical Examination: Moderately obese. Blood pressure 138 mm. Hg systolic and 86 mm. diastolic; pulse 100; temperature 100° C. The heart was normal in size and the sounds were of good quality. There was a diastolic gallop at the apex. There were no murmurs and the rhythm was regular. There were a few fine râles at the lung bases.

Laboratory Data: Examination of the blood was normal. Kahn test was negative. Roentgenograms: chest normal; stag-horn calculus in the left kidney, calculus in the lower right ureter. Serum calcium was 10.9 mg. per 100 c.c. Repeated electrocardiograms throughout the course were identical and showed evidence of old anterior and posterior infarction.

Course: Urinary symptoms cleared rapidly on chemotherapy, but pyuria and hematuria persisted. The patient was afebrile after the first week, and pulse rate was within normal limits thereafter.

Two weeks after entry he had an episode of coronary insufficiency lasting several hours. In the fourth and fifth weeks, he had two episodes of transient aphasia and right hemiparesis lasting a few hours. Following a small pulmonary infarct, femoral vein ligation was performed. Most of this time was spent in bed, and on a dietary regimen he lost 20 pounds.

Three months after entry, administration of propylthiouracil, 250 mg. every six hours, was commenced. Exercise tolerance remained essentially unchanged until seven weeks after therapy was begun, when it rose to 42 trips from a pretreatment maximum of 22. During the next month it slowly rose to a maximum of 68 trips before onset of chest pain, without change in basal metabolic rate or protein-bound iodine level. After 14 weeks he was sent home, with an increase of the drug to 1,500 mg. daily. He had no chest pain, and his activity tolerance was slightly increased.

After five months of therapy he had developed puffiness of the eyelids, fullness of the face and slight enlargement of the thyroid gland. There was essentially no change in his exercise tolerance of December 18, when his protein-bound iodine was 3.2 micrograms, and of January 31, when it was 0.4 microgram. A basal metabolic determination was not done on this date because of technical difficulties.

On February 5, he reëntered the hospital because of severe chest pain lasting several hours. Electrocardiogram showed no change. He was kept in bed and was asymptomatic. On February 9, he died suddenly.

Summary: Angina had been present eight and one-half years before administration of propylthiouracil. Slight improvement in exercise tolerance occurred after seven weeks of therapy, before any change was noted

in the basal metabolic rate or serum iodine level. Despite production of myxedema, there was no additional improvement.

Case 6 (chart 6). A 49 year old man entered the hospital on September 11, 1947. Four and one-half years before entry he first noted midchest oppression on exertion lasting a few minutes to half an hour. He stopped working, but pain occurred after less and less effort and finally at rest.

For four years prior to entry his exercise tolerance was essentially unchanged. Angina occurred on walking 40 feet on level ground, and awakened him two or three times nightly. Nitroglycerin was used eight to 10 times daily.

Physical Examination: Blood pressure 125 mm. Hg systolic and 84 mm. diastolic; pulse 80. No significant findings. The heart was normal in size, sounds were of good quality, there were no murmurs, and the rhythm was regular. The lungs were clear.

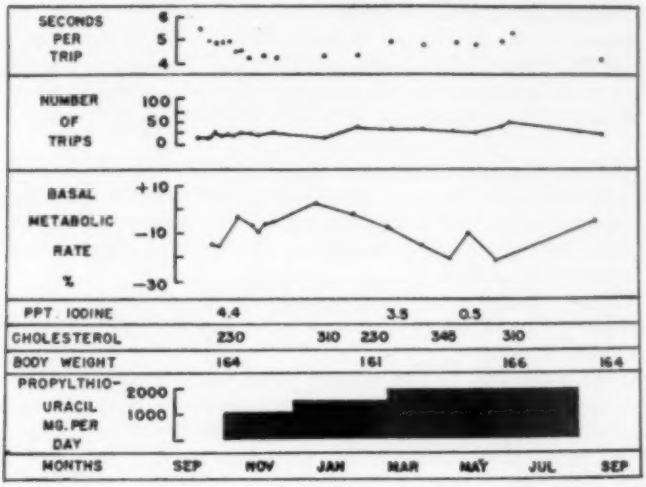

CHART 6. Case 6.

Laboratory Data: Examination of the blood and urine was normal. Kahn was negative. Wintrobe sedimentation rate was 18 mm. per hour. Electrocardiogram was normal and did not change throughout the course. Roentgenograms of the chest and spine were normal.

Course: For one month he was observed without treatment. Maximum exercise tolerance was 24 trips. The basal metabolic rate was minus 15.

On October 14, administration of propylthiouracil, 250 mg. every six hours, was commenced. This was increased to 1,400 mg. daily in December. His metabolic and clinical status was unchanged during this time, with several attacks of pain daily on exertion and at rest. He was discharged in December. The thyroid became slightly enlarged early in February. Propylthiouracil was increased to 2,000 mg. daily in March. The thyroid was very considerably enlarged by the end of April and a bruit was heard. There was definite edema of the lower lids. The protein-bound iodine had dropped to 0.5 microgram and the basal metabolic rate to minus 20. By June, the facial features were puffy and the skin of the hands somewhat dry. Angina pectoris continued, with no change in the daily number of attacks.

On August 15, he stopped medication because he was discouraged. When he was seen on September 3, all signs of myxedema had disappeared, and the thyroid gland was barely palpable. The daily frequency of his angina had not changed.

Summary: Angina had been present for four and one-half years before administration of propylthiouracil. Despite production of myxedema after seven months of therapy, no significant change was produced in exercise tolerance or the frequency of angina pectoris.

Case 7 (chart 7). A 58 year old man entered the hospital on April 14, 1947. Twelve years before entry he had first developed angina pectoris on exertion. In 1937, 1938 and 1941 he had been hospitalized because of severe attacks of prolonged chest pain. The pain was substernal, radiating to the left arm or neck and relieved by nitroglycerin. It occurred on walking 25 to 100 yards on level ground at a moderate pace, or on climbing six to eight steps. Attacks of pain varied in frequency from three daily to three weekly. Activity tolerance was definitely less in the few months prior to entry.

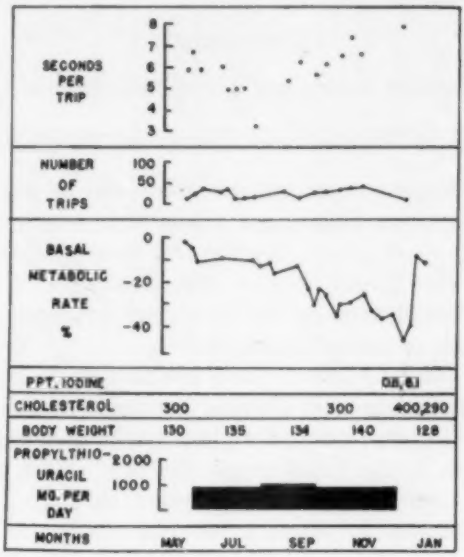

CHART 7. Case 7.

Physical Examination: Blood pressure 160 mm. Hg systolic and 90 mm. diastolic; pulse 80. The heart was normal in size, sounds were of good quality, there were no murmurs, and the rhythm was regular. The lungs were clear.

Laboratory Data: Examination of the blood and urine was normal. Kahn test was negative. Wintrobe sedimentation rate was 29 mm. per hour, and remained unchanged throughout his course. Roentgenogram of the chest was negative. Electrocardiogram at rest showed evidence of old posterior myocardial infarction, and remained unchanged throughout the course. With production of angina pectoris by exercise, there was marked depression of ST segments in limb leads and CF_4.

Course: For six weeks he was observed without treatment. Maximum exercise tolerance test was 32 trips. Basal metabolic rate was minus 10. He had an average of four attacks of angina pectoris daily on slight exertion and at rest. In June, administration of propylthiouracil, 800 mg. daily, was commenced. In the third month of therapy it was increased to 1,000 mg. daily for several weeks, and then decreased to 800 mg.

The basal metabolic rate began definitely to drop at the end of the third month and reached minus 46 after six months. By the fifth month, there were definite edema of the eyelids, puffiness of the face, some enlargement of the thyroid gland, and weakness.

There was no significant change in frequency of angina pectoris, and no change in the exercise tolerance test. On December 11, propylthiouracil was discontinued, at which time the protein-bound iodine was 0.8 microgram and the basal metabolism was minus 38. Two weeks later, all signs of myxedema had disappeared, protein-bound iodine was 6.1 micrograms, and basal metabolic rate minus 6.

Summary: Angina had been present for 12 years before administration of propylthiouracil. Despite the production of pronounced myxedema after five months of therapy, no change was produced in exercise tolerance or frequency of angina pectoris.

Discussion

The pertinent data in these cases are summarized in table 1.

The Effect of Propylthiouracil on Thyroid Function

Size of Gland: Slight to marked increase in size of the gland appeared in all cases during therapy. Enlargement was first detected at 10 weeks. It became marked in three cases, leading to local discomfort in one. In association with large goiters, bruits became audible.

Astwood [9] has demonstrated in rats that hyperplasia of the thyroid accompanies decrease of its iodine content.

Serum Protein-Bound Iodine: There are no data to indicate how rapidly the serum iodine decreases after thyroid hormone production ceases, but it appears [10] that the decrease may take place weeks or months before there is any marked change in the basal metabolic rate. The delay in metabolic response suggests that the thyroid hormone in the tissues may remain at normal concentrations for some time after the serum level has fallen.[11]

This sequence of events is illustrated by cases 2 and 6.

Basal Metabolic Rate: In four cases the basal metabolic rate began to fall during the second or third month of therapy; in one during the sixth, and in one during the tenth.

Myxedema: Evidence of myxedema appeared within one month of the initial drop of the basal metabolism in four cases and within three months in two cases.

At the time myxedema became clinically apparent, the level of the basal metabolic rate varied widely—from minus 11 in case 3 to minus 35 in case 7.

Serum cholesterol rose significantly in four patients during therapy. In case 3, it exceeded 1,000 mg. per 100 c. c.

In all cases, edema of eyelids was the earliest physical sign of myxedema, soon followed by puffiness of facial features. The skin became dry in all, but there was no apparent effect on the texture of the hair. Sensitivity

TABLE I

Case	Age	Duration Angina, Years	Propyl-thiouracil, mg. Daily	Months of Therapy	Lowest BMR before Therapy	BMR at Onset of Improvement	Months before Onset of Objective Improvement	Months before Appearance of Myxedema	Lowest BMR during Therapy	Lowest Serum Iodine during Therapy (Micrograms)	Maximum Trips prior to Therapy	Maximum Trips during Therapy	Remarks
1	57	2	800–150	17¼	+17%	+1%	2¼	5	−30%	0.7	58, angina	220, no angina	Excellent improvement, 15 months. Accidental drowning.
2	56	7	400–3000	19	−11%	+2%	8½	10½	−29%	0.8	24, angina	300, no angina	Very good improvement, 8 months. Relapse.
3	57	1½	800–400	16½	+3%	−11%	1¾	2½	−38%	0.7	25, angina	300, no angina	Very good improvement, 6 months, partial relapse. Died of coronary disease after restoration of normal BMR with thyroid hormone.
4	58	3	800–400	4¾	−7%	−13%	1¾	3	−40%	1.1	14, angina	300, no angina	Very good improvement, 5 weeks, complete relapse. Dorsal sympathectomy.
5	51	9	1000–1500	5	−11%	−8%	1¾	5		0.4	22, angina	68, angina	Slight improvement. Died of coronary disease while under treatment.
6	49	4½	1000–2000	10	−15%			6½	−19%	0.5	24, angina	42, angina	Treatment stopped. Failure.
7	58	12	800–1000	6	−10%			5	−46%	0.8	32, angina	39, angina	Treatment stopped. Failure.

to cold occurred in one case, moderate lassitude and fatigability in five. Lacrimation, after appearance of periorbital edema, was somewhat annoying in two patients. In three, there was a gain in weight of from five to 20 pounds.

All patients whose angina was improved stated emphatically that any discomfort caused by myxedema was very tolerable in exchange for the increased range of activity and freedom from pain.

Electrocardiograms showed no changes attributable to myxedema, and there was no change in heart size by roentgen-ray. There were no significant changes in blood pressure or pulse rate.

When propylthiouracil was discontinued, evidences of goiter and myxedema disappeared within two to four weeks.

Improvement in Exercise Tolerance during Therapy with Propylthiouracil

Improvement began during the second or third month of therapy in four cases, and during the ninth month in one. It failed to occur in two patients even though myxedema was produced and therapy was continued six and 10 months.

In case 1 improvement was excellent, with restoration to unrestricted activity for 15 months. Exercise tolerance rose from 58 trips with angina pectoris to 220 trips without it.

In case 2 improvement was very good for eight months. The patient was restored to moderate activity, with infrequent pain. Exercise tolerance rose from 24 trips with angina to 300 trips without it. After eight months pain began to occur on less effort, and the exercise tolerance dropped to 65 trips with angina.

In case 3 improvement was quite good for six months, with rise of exercise tolerance from 25 trips with angina to 300 trips without it. A relapse then occurred, although the degree of painless activity remained greater than it had been prior to therapy.

In case 4 there was marked but very transient improvement (five weeks), followed by complete relapse.

In case 5 improvement was slight. The patient died of coronary disease during the fifth month of treatment. Since there were no changes in serum iodine and basal metabolism during improvement, it probably was not related to propylthiouracil.

In cases 2, 3 and 4 it is possible that relapse after improvement might have been due to the progressive nature of the disease, with further circulatory impairment.

Relationship between Depression of Thyroid Function and Improvement in Angina Pectoris

There has been no clear agreement as to the fundamental mechanism of improvement in angina pectoris following total thyroidectomy.

Two and three days following operation in five cases, Eppinger and Levine [12] observed, in most instances, a decreased or absent response of blood pressure and pulse rate to intramuscular injection of epinephrine, and failure to produce angina pectoris in four. They suggested that complete removal of the thyroid gland altered the response of the cardiovascular system to adrenalin, an effect independent of changes in the basal metabolic rate or rate of blood flow.

Sawyer and Brown [13] found that removal of the thyroid gland in cats decreased the rate response of the denervated heart to both injected and secreted epinephrine. They concluded that, in this manner, thyroidectomy might have an influence favorable to the action of the embarrassed heart. Leblond and Hoff [14] have shown that the effect of thyroxine on the heart rate is a direct one for the most part and not the consequence of general metabolic stimulation.

Riseman et al.[15] stated that improvement following thyroidectomy was independent of changes in sensitivity to epinephrine. They found no important differences in the response of pulse rate and blood pressure to epinephrine injected intravenously before and after total thyroidectomy, as long as the basal metabolic rate was above minus 30. The absence of anginal pain immediately after total thyroidectomy was ascribed to the interruption of nerve pathways, and the more permanent relief was coincident with a drop in the basal metabolic rate, which thus relieved the heart of a considerable portion of its burden.

To explain his own results, Raab [2] enlarged upon the theory that decreased thyroid activity lessens the sensitivity of the heart to adrenalin.

In the present report, a correlation is suggested in case 1 between the depression of the metabolic rate and the onset of objective improvement. In case 3 the evidence suggests that improvement began about the time the basal metabolic rate began to drop. A further suggestive correlation is afforded by the increase in angina pectoris with the administration of thyroid hormone and restoration of a normal basal metabolic rate. In case 2 there was no fall in basal metabolic rate at the time of improvement. However, the fall of protein-bound iodine to myxedema level at the time suggests a possible correlation with a decrease in the amount of circulating thyroid hormone. This might also serve to explain the dramatic improvement in case 4 at a time when the drop in basal metabolic rate did not seem very significant (minus 7 to minus 13). Yet, with a further drop to only minus 17, features of myxedema appeared.

It is suggested that the improvement seen in these four cases may be related in some way to a decrease in the amount of circulating thyroid hormone, independent of changes in the metabolic rate.

Administration of Propylthiouracil

In three cases a satisfactory depression of thyroid function was produced by 800 mg. daily; in four, larger doses appeared necessary (1,000 to 3,000

mg. daily). It cannot be definitely stated that increasing the dosage hastened more complete depression of thyroid function, but cases 2, 7, 5 and 6 suggest this may be so. In the latter two, serum iodine had already dropped somewhat on the initial dose. In case 2, however, the decline had leveled off for a month before the larger dose was given.

Case 2 demonstrates that there may be only partial blocking of thyroid function on a six-hour dosage schedule. Frequency of administration as well as size of dose should be considered in any instance where thyroid function fails to be depressed satisfactorily.

The degree of block achieved by a particular treatment schedule could be determined with advantage by the method used in case 2 where facilities for measurement of radioactive iodine uptake are available. Appropriate alterations of the treatment schedule might permit more prompt depression of thyroid function, possibly avoiding protracted treatment as in cases 2 and 6.

It appears that the effective dosage in the individual case must be determined by clinical trial.

It is possible that satisfactory depression of thyroid function might have been accomplished, in some cases, with doses smaller than those employed. It is reported [16] that 75 to 150 mg. daily have caused significant decline in the basal metabolism of euthyroid patients.

Summary and Conclusions

Seven cases of angina pectoris were treated with propylthiouracil. Relief of pain was significant in three, transient in one, slight in one, and absent in two. When benefit occurred, it usually appeared about two months after beginning treatment. Mild to moderate myxedema was produced in all cases. No toxic reactions were encountered, even with large doses (800 to 3,000 mg. daily) for many months.

Evidence suggests that improvement may be related to a decline of the circulating thyroid hormone rather than to general metabolic depression.

The observed results are considered sufficiently suggestive to merit consideration of this therapy where the usual medical measures fail to restore a reasonable degree of painless activity. Dosage should be adjusted and treatment continued until myxedema becomes evident, before the therapy is abandoned as ineffective.

Acknowledgment

The author is indebted to Dr. Douglas Riggs, of the Harvard Medical School, for the determinations of the serum precipitable iodine.

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THE ASSOCIATION OF NODULAR GOITER WITH THORACIC PAIN: REPORT OF SEVEN CASES*

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In 1938 we reported [1] the case of a 45 year old woman with a nontoxic intrathoracic nodular colloid goiter who suffered severe attacks of thoracic and left shoulder pain, with abnormal T waves in the chest leads of her electrocardiogram. Following the removal of the goiter the attacks of pain diminished in frequency and severity and disappeared in about 17 months; the electrocardiogram returned to normal. It is our purpose here to report a 13 year postoperative follow-up on this patient. We also wish to describe briefly six other patients in whom we have observed the association of various types of thoracic pain and nodular goiter, with or without concomitant evidence of heart disease, and in whom the thoracic pain was modified or relieved after thyroidectomy.

Case Reports

Case 1. (The details of this case have been reported previously.[1])

The patient was a white woman, 45 years of age when first seen in November, 1935. At that time she complained of attacks of pain which had begun abruptly three weeks before. The pain was accompanied by a sense of tightness, and involved simultaneously the left upper chest, the left side of the back down to the waist, the left shoulder, the inner side of the left arm to the elbow, and the left side of the neck, including the jaw. The pain was almost always nocturnal, bore no relation to effort, excitement or swallowing, and occurred usually while she was sitting quietly or while lying in bed. The attacks lasted from 30 minutes to 12 hours. She could sometimes get relief by walking about the room. Physical examination was essentially negative. Roentgenograms showed a large substernal mass apparently in close contact with the aortic arch. The electrocardiogram showed inversion of T waves in all precordial leads but was otherwise normal. There was no evidence of thyrotoxicosis. The basal metabolic rate was − 9 per cent, the serum cholesterol 250 mg. per 100 c.c. In January, 1936, a large intrathoracic goiter was removed by Dr. Benjamin Lipshutz at the Mt. Sinai Hospital. The excised tissue weighed 80 gm. and contained numerous areas of increased colloid deposition with flattening of acinar epithelium.

Following operation, the attacks of pain decreased promptly in frequency and severity. Mild attacks occurred every two to four months until June, 1937 (about 17 months after operation) when they ceased altogether. In October, 1937, the electrocardiogram had returned to a normal pattern.

The patient remained well until April, 1941, when she began to complain of precordial pain extending into the left arm and (unlike the thoracic pain prior to thyroidectomy) occurring only on exertion. This effort angina increased in frequency and severity and in December, 1941, myocardial infarction occurred with electrocardiographic evidence of involvement of the anterior wall of the left ventricle.

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Convalescence was satisfactory and by February, 1942, the electrocardiogram had returned to normal. Since that time she has had occasional slight vague pain in the chest and shoulders, but no symptoms suggestive of angina pectoris and no complaints similar to her preoperative attacks. She was last examined January 5, 1949, approximately 13 years after her thyroidectomy. At that time she showed moderate obesity, hypertension (blood pressure 190 mm. Hg systolic and 90 mm. diastolic), with a soft systolic basal murmur and slight accentuation of the aortic second sound. Roentgenogram of the chest showed a slight increase in the transverse diameter of the cardiac shadow and slight elevation of the right diaphragm. The mediastinum was normal. The electrocardiogram showed slight inversion of the T waves in Leads I, II and CR 5.

Comment: This patient's original attacks of pain extended into the left arm and left neck but bore no relation to effort, although the electrocardiogram was somewhat abnormal. The attacks gradually disappeared after the removal of a large nontoxic intrathoracic goiter, ceasing altogether 17 months after operation. About four years after operation typical angina pectoris appeared, culminating in myocardial infarction. Following recovery from this, there has been no further significant thoracic pain. The original attacks of pain have not recurred 13 years after thyroidectomy.

Case 2. A 34 year old Negro woman was first seen on February 20, 1934, complaining of fatigability, shortness of breath, palpitation, pain in the chest and dryness of the skin. These symptoms had been present, with gradually increasing intensity, for about five years. The palpitation and dyspnea occurred only on effort and were of moderate intensity. The patient gave varying descriptions of the thoracic pain, and its pattern appeared to be inconstant. At times she described it as a dull precordial pain following effort and spreading into both shoulders, with immediate relief upon cessation of activity; at other times there was a sense of pressure and a sticking pain behind the upper sternum, which occurred without relation to effort or swallowing, came and went without apparent cause, and was often nocturnal. There were occasional choking and dysphagia.

Examination showed moderate obesity (height 60 inches, weight 151 pounds), scanty hair on the scalp, eyebrows and axillae, and some dryness of the skin. She was somewhat dull and apathetic. The blood pressure was 114 mm. Hg systolic and 76 mm. diastolic. There was moderate, diffuse, bilateral, slightly irregular enlargement of the thyroid gland, without physical signs of substernal extension. Physical examination of the heart showed no abnormality. The basal metabolic rate was — 16 per cent. The total serum cholesterol was 250 mg. per 100 c.c. The electrocardiogram was normal. Roentgenogram of the chest showed subclavicular extension of the thyroid on the left side, but was otherwise negative. A diagnosis of nodular goiter with mild hypothyroidism was made, and desiccated thyroid was prescribed in doses of 60 mg. daily.

The patient was irregular in clinic attendance. She was seen several times in 1935, but did not return again until May, 1939, at which time she reported an increase in the severity of the choking sensation and the sticking pain behind the upper sternum. After several visits to the clinic she disappeared again until April, 1940, when she reported continued progression of these symptoms. At this time the basal metabolic rate was — 16 per cent, her weight had increased to 164 pounds, and the goiter had increased in size.

A subtotal thyroidectomy was performed on September 20, 1940. At this time the basal metabolic rate was — 14 per cent and the electrocardiogram was normal.

The thyroid showed a diffuse multinodular enlargement which partially encircled the trachea on both sides and presented a moderate subclavicular extension on the left. The excised portions measured 9 by 4 by 3 cm., 6 by 4 by 3 cm. and 3 by 2 by 2 cm., respectively. The pathologic diagnosis was nontoxic nodular goiter.

The thoracic pain, palpitation and dyspnea disappeared a few days after the thyroidectomy. The patient was last seen January 5, 1949, about eight and a quarter years after operation. She reported that there had been no recurrence of the thoracic pain or cardiac complaints. Her weight had increased to 187 pounds, her blood pressure was 160 mm. Hg systolic and 104 mm. diastolic. She was somewhat sluggish, with rather dry skin and hair and slight keloid formation in the thyroidectomy scar. There was no recurrence of the goiter. Roentgenogram of the chest was negative, except for some tortuosity of the aorta. Physical examination of the heart was negative. The electrocardiogram showed slight inversion of the T waves in Leads I and CR 4 and 5, and flat T waves in Lead II. The basal metabolic rate was — 16 per cent, the serum cholesterol 384 mg. per 100 c.c.

Comment: This patient had a nodular goiter with slight subclavicular extension and mild hypothyroidism. Her thoracic pain appeared to combine two components—precordial pain on effort, associated with palpitation and dyspnea and extending into the shoulders, and a localized high retrosternal pain occurring without apparent cause. Both components disappeared promptly after thyroidectomy and have not recurred after eight and a quarter years. During this time she has become moderately hypertensive and her electrocardiogram has become abnormal.

Case 3. A 50 year old Negro woman was first seen on April 26, 1940. She had first noticed an enlargement of the neck 17 years before. This had remained essentially unchanged in size, but became temporarily more noticeable when she coughed during the course of frequently recurring colds in the head and chest. During these 17 years she had been under observation in the Out-Patient Clinic of the Henry Phipps Institute, but no evidence of tuberculosis had been found. There had been no weight loss or other symptoms suggestive of thyrotoxicosis. For two years she had noted occasional brief attacks of thoracic pain which occurred without apparent cause and with no relation to effort, excitement, eating or drinking or respiratory infection. The pain extended from the upper dorsal spine through the middle of the chest to the sternum. It was rather dull and boring in character, came on abruptly, usually lasted five to 10 minutes and then disappeared promptly. The attacks occurred at intervals of one to two months and were practically always diurnal. There had been slight dyspnea and palpitation on effort for about two years.

Physical examination showed a firm nodule about the size of a walnut in the region of the left thyroid lobe, adjacent to the trachea. The blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. Physical examination of the heart and lungs was negative. There was no evidence of thyrotoxicosis. Roentgenogram of the chest showed a large circumscribed mass in the right upper mediastinum causing displacement of the trachea and esophagus posteriorly and to the left; heart and lungs were negative. The basal metabolic rate was + 18 per cent. The electrocardiogram showed slight slurring of QRS complexes and slightly low T waves in all limb leads. A subtotal thyroidectomy was performed on June 5, 1940, by Dr. E. L. Eliason. A completely substernal mass about the size of a lemon was removed from the right upper mediastinum and several smaller nodules were removed from the lower portion of the left lobe. The excised portions measured 8 by 4 by 3 cm. and 11 by 6 by 4 cm., respectively. The pathologic diagnosis was nontoxic nodular

goiter (colloid nodules) with partial calcification. The patient had no attacks of pain during her hospital stay. Six days after operation the basal metabolic rate was − 11 per cent and the electrocardiogram was unchanged.

The patient was last seen on January 6, 1949, about eight and one-half years after her operation. Her basal metabolic rate at that time was 0. Her electrocardiogram was normal and roentgenogram of the chest showed no abnormality of the heart or lungs. The operative scar was well healed and there was no recurrence of the goiter. The blood pressure was 140 mm. Hg systolic and 80 mm. diastolic. The patient stated that she had had two or three mild, brief attacks, similar to the preoperative episodes, during the year following her thyroidectomy. The attacks had then ceased and she had subsequently remained symptom free.

Comment: This patient's goiter had been present for about 17 years, during the last two of which she had suffered occasional attacks of dull boring pain extending from the upper dorsal spine through to the sternum and occurring without apparent cause. There was no evidence of thyrotoxicosis or cardiovascular disease. Following the removal of a large nodular goiter with a lemon sized substernal extension, the attacks gradually diminished and disappeared after a year.

Case 4. A 67 year old white woman was first seen on June 9, 1940. For about five years she had been under medical supervision because of "heart trouble." Her cardiac symptoms had included periodic bouts of dyspnea, palpitation, cough and edema of the feet. These symptoms had always been relieved by bed rest for a few days. She had taken digitalis intermittently in unknown amounts. However, her attacks of dyspnea and palpitation had increased in frequency and severity during the past year. For about six weeks she had suffered frequent attacks of dull constricting pain which originated behind the upper sternum and spread downward into both breasts and straight through to the upper dorsal region. The pain began without relation to effort, but was often intensified by exertion once it had begun. It was usually diurnal, but bore no relation to excitement, eating or drinking. It spread slowly and usually persisted with gradually decreasing intensity for several hours. The attacks occurred almost daily. Physical examination showed a firm nodular mass about the size of a lime in the region of the left thyroid lobe, with percussion changes indicative of intrathoracic extension. The systolic blood pressure varied from 160 to 180, the diastolic from 90 to 100. Cardiac dullness was slightly increased to percussion. The heart rate was normal. The rhythm was regular except for occasional extrasystoles. Systolic murmurs were audible over the base and apex. There was slight edema of the lower legs and feet. Roentgenogram of the chest showed slight enlargement of the cardiac shadow and slight dilatation of the ascending aorta. The superior mediastinum was occupied by a large dense mass which displaced the trachea and esophagus to the left. The electrocardiogram showed occasional extrasystoles and the P waves were inverted in Lead II. The PR interval varied from .16 to .20 second (wandering pacemaker). The QRS complexes were of normal duration, slightly slurred in all leads, while the T waves were upright in all leads. The ST interval was depressed in Leads I and II. These changes were considered compatible with the effect of the digitalis which she had been taking. The basal metabolic rate was + 18 per cent. There was moderate anemia (hemoglobin 70 per cent).

On June 24, 1940, a subtotal thyroidectomy was performed by Dr. E. L. Eliason. Most of the goiter lay within the thorax and consisted of multiple nodular areas with gross degenerative changes. The excised mass measured 12 by 6 by 5 cm. The histologic diagnosis was spindle cell carcinoma of the thyroid. The patient's immediate postoperative course was satisfactory. The attacks of substernal pain dis-

appeared promptly. However, six weeks after operation a recurrent nodular mass appeared in the neck, and this was soon followed by increasing evidence of tracheal and esophageal compression by a rapidly growing recurrence in the neck and mediastinum. Irradiation was ineffective and the patient died four months after operation.

Comment: This patient's cardiac symptoms had been present for about five years, but for about the last six weeks there were increasingly severe attacks of dull retrosternal pain, not anginal in character. These attacks disappeared following the removal of a large carcinomatous goiter with intrathoracic extension, and did not recur despite the subsequent development of severe dyspnea and other symptoms of tracheal compression which followed recurrent growth of the carcinoma.

Case 5. A 47 year old white woman was first seen on September 18, 1940. Her complaints were numerous, but the principal one was pain in the upper chest. At the age of 19 she had noted a swelling of the neck after the birth of her first child; this disappeared following local application of a salve. In April, 1940, menstruation had ceased after a gynecologic operation. A number of symptoms had appeared at this time and had persisted. These included coronal headache, dyspnea, palpitation, choking and dysphagia, nervousness, anorexia, sweating and insomnia. There had also been increasing enlargement of the neck. The pain in her chest was described as continuous, burning and located behind the upper sternum. From this area it sometimes spread straight through to the dorsal spine, and sometimes bilaterally into the infraclavicular spaces. It was not related to excitement, effort, position or the ingestion of food or liquid. It had shown some spontaneous variation in intensity, but was not relieved by medication. Her diet was inadequate and she had lost 20 pounds since the onset of her symptoms.

Physical examination showed fairly good nutrition, excessive nervousness and apprehension, and a slight tremor of the hands. The thyroid showed a diffuse, somewhat irregular, fairly marked bilateral enlargement of rather soft consistency, containing several scattered nodular areas. There was no definite physical sign of substernal extension. The cardiac rate was moderately accelerated but the rhythm was regular. The blood pressure varied from 130 to 190 systolic and from 80 to 110 diastolic. The basal metabolic rate was — 1 per cent. The electrocardiogram showed left axis deviation and a Q wave in Lead III. A roentgenogram of the chest showed substernal extension of the thyroid, with several calcified areas within the thyroid shadow; the aorta was slightly increased in width, and the cardiac silhouette was slightly increased in area.

On September 25, 1940, a subtotal thyroidectomy was performed by Dr. E. L. Eliason. The goiter was multinodular and fairly large. No substernal extension was found at operation, although the lateral lobes partially encircled the trachea and esophagus. The two portions removed measured 8 by 5 by 3 cm. and 7 by 4 by 3 cm., respectively. The pathologic diagnosis was nontoxic nodular goiter with multiple adenomas and areas of calcification. The patient's postoperative course was uneventful.

She was reëxamined on September 22, 1941. At that time she reported that the retrosternal pain had disappeared for two weeks immediately following operation, after which it had recurred and persisted in its original form. The dysphagia and choking had disappeared, but her other symptoms remained essentially unchanged. The basal metabolic rate was — 10 per cent. Roentgenograms of the chest were reported as negative. The electrocardiogram no longer showed left axis deviation, but a small Q_3 wave was still present.

The patient was last examined on October 27, 1948, about eight years following her thyroidectomy. At this time she stated that her original retrosternal pain had finally disappeared about two years after her operation. She was still highly nervous and had frequent bouts of dyspnea and palpitation, which were sometimes accompanied by a dull precordial pain or discomfort.

Examination of the heart showed a somewhat variable but moderate tachycardia, with a systolic basal murmur and some accentuation of the second aortic sound; there was no cardiac enlargement. The blood pressure was 176 mm. Hg systolic and 90 mm. diastolic. The electrocardiogram was within normal limits. Roentgen examination of the chest showed nothing abnormal except spasm in the cardiac end of the esophagus.

Comment: This patient was highly nervous and emotional, with intermittent tachycardia and hypertension, but was not thyrotoxic. Her diffusely nodular goiter did not show substernal extension, although this had been suggested in the roentgenogram. Her burning retrosternal pain was not related to effort. It disappeared for two weeks following thyroidectomy, but recurred and did not finally disappear for about two years. When last seen eight years after operation she had been free of pain for about six years.

Case 6. A 54 year old white male was first seen on September 21, 1944, complaining of attacks of pain in the chest which had begun about three years previously. The attacks frequently occurred during bed rest or soon after arising. They sometimes followed meals or excitement. They were often induced by exertion, but the pain would frequently subside after he had walked a short distance and he could thereafter continue to walk indefinitely without pain. Nitroglycerin gave occasional slight relief. The pain began at times behind the lower sternum, was burning in character, and spread sometimes over the right, sometimes over the left anterior chest. At other times it began behind the upper sternum and spread either to the right or to the left shoulder. It was occasionally accompanied by slight dyspnea. There was no dysphagia, cough or expectoration. He worked under considerable tension as a labor organizer, and smoked about 40 cigarettes daily. He had been studied by several physicians, and reported that his electrocardiograms and basal metabolism determinations had been within normal limits on several occasions. Roentgenograms of the chest, however, had shown a large mass occupying the right upper portion of the mediastinum.

Physical examination showed little of importance. The patient was moderately obese (weight 178 pounds, height 65.5 inches), blood pressure 138 mm. Hg systolic and 80 mm. diastolic. No masses were palpable in the neck. The trachea was deviated to the left, the percussion note was somewhat impaired in the right interscapular space, and coarse râles and rhonchi were audible in this area. There was no clinical evidence of thyrotoxicosis.

Further studies were conducted at Temple University Hospital under the direction of Dr. W. Wayne Babcock and Dr. Hugo Roesler. These showed the basal metabolic rate to vary from + 21 to + 30 per cent; roentgenograms of the chest confirmed the previous finding of a right substernal mass, but were otherwise negative; the electrocardiogram showed left axis deviation, with Q waves in Leads I, CR 4 and 5, and slight depression of S–T segments in limb leads and CR 4 and 5.

On October 10, 1944, Dr. Babcock removed a substernal goiter which weighed 109 gm. and which extended down close to the aortic arch on the right side. Histologic examination showed mixed changes, with scattered adenomatous foci, areas of colloid involution and other areas showing hyperplasia. The patient was com-

pletely free of attacks for four days after operation. Thereafter he experienced occasional attacks of mild to moderate severity during bed rest or upon exertion.

He was last seen on January 12, 1949, four years and three months after his operation. At this time he described himself as 50 per cent improved. The attacks of pain had ceased to occur at night, and were seldom induced by excitement or eating. Exertion still produced attacks frequently, but the pain was milder and occurred only behind the upper sternum, with extension into the left infraclavicular space. His weight was unchanged and the blood pressure was 148 mm. Hg systolic and 90 mm. diastolic. Physical examination was essentially negative except for his thyroidectomy scar. The roentgenogram of the chest was negative. The basal metabolic rate was + 15 per cent. The electrocardiogram was normal.

Comment: This patient's thoracic pain was probably, in large part, of cardiac origin. It was markedly ameliorated by the removal of an intrathoracic goiter, which may have been mildly toxic, although this diagnosis remains doubtful. The pattern of the thoracic pain was altered following thyroidectomy, and certain components of it had disappeared entirely four and one-half years after operation.

Case 7. A 52 year old white male was first seen on June 24, 1948, by Dr. C. C. Wolferth, complaining of attacks of pain in the left shoulder and chest which had begun only two weeks previously. The pain occurred chiefly at night and was not related to exertion, eating or excitement, nor was it accompanied by dyspnea. It began in the left shoulder and spread downward over the precordium. The pain was described as severe and knifelike and occurred two to four times daily, lasting two to three minutes at a time. The patient worked under some tension as superintendent of a cleaning and dyeing plant and smoked 20 cigarettes daily.

Physical examination revealed nothing of importance except slight hypertension 175 mm. Hg systolic and 80 mm. diastolic. The electrocardiogram showed slight negative RS–T segment displacement in precordial leads. The T waves were slightly diphasic in Lead 11 and flattened in CR 5. These changes were considered suggestive of a myocardial lesion involving the posterolateral wall of the left ventricle. The orthodiagram showed slight enlargement of the cardiac silhouette to the left and an area of increased density in the right upper mediastinum. Subsequent roentgenograms showed this density to be caused by a large circumscribed substernal mass which lay immediately adjacent to the aortic arch, and which displaced the trachea and esophagus posteriorly and to the left. A second electrocardiogram made two weeks after the first one was within normal limits, but the original abnormalities were consistently found in a series of subsequent tracings. The patient's symptoms failed to respond to a variety of therapeutic measures, which included rest, sedation, abstinence from tobacco, papaverine, narcotics, so-called coronary vasodilators, and a course of roentgen therapy to the substernal mass. There was no change in the size of the substernal mass following irradiation. There was no clinical evidence of thyrotoxicosis.

On September 3, 1948, Dr. Julian Johnson removed a large substernal goiter weighing 170 gm., which extended down to the aortic arch. Histologic sections showed nontoxic nodular goiter with multiple adenomas. The original attacks of pain disappeared after operation and never recurred. However, before his discharge from the hospital on September 11 another symptom complex appeared. This consisted of steady severe pain, occurring chiefly at night and lasting from five to 45 minutes. It began below the left scapula and spread to the left shoulder, down the left arm and sometimes directly through to the precordium and retrosternal area. It was not brought on by exertion or food, nor was it relieved by nitrites. An electrocardiogram on October 29 showed evidence of damage in the anteroseptal

region of the left ventricle; roentgenogram of the chest on that date was negative. Because of increasing severity of the postoperative pain syndrome, patient was readmitted to the hospital December 17, 1948. Roentgenograms of the chest showed nothing abnormal except a slight left lateral scoliosis of the upper thoracic spine. The pain was relieved for about three hours following a left paravertebral root block from T 3 to T 6 with metacaine. On January 6, 1949, the electrocardiogram showed definite evidence of myocardial infarction involving the posterior wall of the left ventricle. The patient's pain disappeared on January 10, and electrocardiograms taken on January 12, 19 and 25 showed evidence of progressive healing of the infarction. He remained free of pain and by January 27 was allowed bathroom privileges. On this date he was found dead in the bathroom early in the morning. Necropsy was not permitted.

Comment: The relationship between this patient's intrathoracic goiter and the attacks of pain is uncertain. The original attacks were certainly not typical of coronary artery disease and they disappeared immediately after operation. His postoperative pain syndrome was likewise not typical of coronary artery disease, but disappeared soon after electrocardiographic evidence of a posterior myocardial infarction was found, and the patient doubtless succumbed to a cardiac catastrophe.

Discussion

Pertinent data in our cases are summarized in table 1.

In six of the seven patients the original attacks of pain disappeared completely after thyroidectomy. In three instances relief occurred within two weeks; in the others the attacks gradually subsided over periods extending up to two years after operation. Two of these patients suffered myocardial infarction six years and four and one-half months, respectively, after operation, but in both of these patients the pattern of the anginal pain associated with these infarctions differed from that observed prior to thyroidectomy. The latter (case 7) undoubtedly had coronary artery disease prior to thyroidectomy; the former (case 1) had an abnormal electrocardiogram before operation which subsequently returned to normal before her infarction occurred. The one patient whose symptoms did not completely disappear presented strong evidence of myocardial (coronary) disease, and may also have been mildly thyrotoxic.

It will be seen from table 1 that the pain varied considerably in character and distribution. It tended usually to occur without apparent cause, although in three cases it was at times precipitated or intensified by effort or eating. In two cases it was predominantly nocturnal, and in one of these patients (case 1) was sometimes relieved by physical activity. There was also considerable variation in the rapidity with which the attacks disappeared after thyroidectomy. In five patients the goiter was first discovered during examination for thoracic pain. The other two patients had had known goiters for 17 and approximately 28 years, respectively. The goiter was entirely intrathoracic in three cases, partially intrathoracic in three, and cervical in one.

TABLE I

Clinical Data in Seven Cases of Nodular Goiter and Associated Thoracic Pain

Case Number	Sex	Age at Onset of Symptoms	Pain					Heart Disease	Thyroid Gland	Duration of Goiter Before Symptoms
			Character	Distribution	Occurrence	Precipitating Factors	Postoperative Course			
1. R. S.	F.	45	Lancinating or constricting	Left hemithorax, neck, shoulder, scapula, lower jaw, inner aspect left upper arm	Nocturnal chiefly	None demonstrable	Marked decrease, complete disappearance after 17½ months	Doubtful before operation. Myocardial infarction 6 years later	Nontoxic nodular colloid goiter	Unknown
2. S. R.	F.	29	Dull, precordial, sticking, retrosternal	Precordium, radiating to shoulders. Localized behind upper sternum	Diurnal and nocturnal	Precordial pain sometimes precipitated by effort	Complete relief a few days after operation	None demonstrable	Nontoxic nodular goiter. Possible mild postoperative hypothyroidism	Unknown
3. F. B.	F.	48	Dull or boring	Mid-thoracic spine through chest to sternum	Diurnal	None demonstrable	Two or three mild attacks in 1st postoperative year; none thereafter	None demonstrable	Nontoxic nodular goiter	17 years
4. A. B.	F.	67	Dull constricting	Retrosternal, radiating into breasts and dorsal spine	Diurnal	Intensified by exertion	Disappearance several days after operation	Probable	Carcinoma of thyroid	Unknown
5. R. C.	F.	47	Burning	Retrosternal, radiating to dorsal spine and both infraclavicular spaces	Continuous	None	Disappearance 2 years after operation	Probably none	Nontoxic adenoma. No intrathoracic extension	Probably 28 years
6. M. S.	M.	51	Burning	Retrosternal, radiating bilaterally to anterior chest and shoulders	On arising or after meals	Exertion and occasionally eating	Marked improvement but not complete disappearance after operation	Probable	Adenomas and colloid nodules. Possible mild thyrotoxicosis	Unknown
7. M. L.	M.	52	Lancinating	Left shoulder radiating to precordium	Nocturnal	None demonstrable	Immediate postoperative relief followed by posterior thoracic pain culminating in myocardial infarction	Coronary artery disease with postoperative myocardial infarction	Nontoxic adenomas	Unknown

Relationship between the goiter and the attacks of thoracic pain in these cases is obscure. The disappearance or amelioration of the pain after thyroidectomy certainly suggests a causal relationship, despite the fact that the pain disappeared promptly after operation in only three patients. Possible factors which may be entitled to consideration in an attempt to explain the relationship may be listed as follows, although it is obvious that none of the suggestions listed below is applicable to all of our cases:

1. As suggested in our previous report,[1] thyroidectomy may have affected the perception of pain impulses generated in the heart or aorta by interrupting afferent impulses transmitted through branches of the vagus and the superior and middle cardiac nerves which communicate with the innervation of the thyroid. Weinstein and Hoff [2] have confirmed the intimate relationship between the superior and middle cardiac nerves and the sympathetic innervation of the thyroid, and suggested that interruption of these communications might explain the beneficial effect of total thyroidectomy in certain cases of angina pectoris.

2. The intrathoracic mass of the substernal goiter may have produced pain by direct pressure on the periaortic portion of the superficial cardiac plexus (case 1).

3. Compensatory scoliosis of the cervical or upper dorsal spine, developing to accommodate the spatial requirements of the growing intrathoracic goiter, may have contributed to the thoracic pain by producing muscle spasm or pressure on spinal nerve roots (case 1).

4. The development of post-thyroidectomy hypothyroidism may have relieved pain of cardiac origin by a mechanism analogous to that suggested by Blumgart and his associates [3] following total thyroidectomy in selected cases of angina pectoris (case 2).

5. Thyroidectomy may have eliminated an agent produced by the thyroid gland, capable of producing a specific cardiotoxic effect with the development of cardiogenic pain, but without the production of thyrotoxicosis. This concept raises again the question of the existence of a specifically cardiotoxic thyroid hormone or abnormal thyroid product. Despite a good deal of suggestive clinical and experimental evidence, it must be conceded that the existence of such an action by the thyroid is not adequately supported by presently available data. In this connection, recent efforts to correlate the physiologic activity of various types of thyroid nodules with their histologic structure by means of radioautographs with the use of radioactive iodine are of interest. Dobyns,[4] in reporting such studies, has implied that mild symptoms of thyrotoxicosis and cardiac strain might occasionally be produced by such hyperplastic nodules without elevation of the basal metabolic rate, but with symptomatic improvement after excision of the nodular areas. Our patients were encountered before radioautographs were available, and the demonstration of such a factor in the production of their symptoms was not possible.

6. The pain might have been produced by direct pressure of the goiter upon the trachea, esophagus or other cervical or mediastinal structures. Against this possibility is the absence of other symptoms of tracheal, esophageal and mediastinal pressure in our cases (except in case 2 and in case 4 only after operative relief of pain). Against it also is our failure to observe similar types of pain in patients with other mediastinal tumors.

Summary and Conclusions

1. Seven cases are described in which nodular goiter occurred with coexistent thoracic pain of variable pattern. In six of the seven cases the goiter was partially or entirely intrathoracic. In six of the seven cases there was no evidence of thyrotoxicosis, and in the remaining case the existence of thyrotoxicosis was extremely doubtful. Evidence of coexistent myocardial (coronary artery) disease was present in two cases.

2. Following subtotal thyroidectomy, the original thoracic pain either disappeared entirely or was materially modified in all our patients. The time required for disappearance or amelioration of the pain varied from a few days to two years after operation. Two patients developed myocardial infarction four and one-half months and six years, respectively, after operation, but the pattern of the anginal pain and that accompanying the infarction in both these patients differed from that observed prior to thyroidectomy.

3. Although no explanation is presently available by which the goiter may be linked with the thoracic pain in these cases, a causal relationship seems likely. Six possible factors which might be involved in such a relationship are mentioned.

4. Nodular cervical or intrathoracic goiter should be considered as a possible etiologic or complicating factor in patients with thoracic pain, particularly when the character of the pain and its distribution and mode of onset suggest an atypical form of angina pectoris.

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THE RELATION OF HYPERPLASTIC ARTERIOSCLEROSIS TO DIABETES MELLITUS*

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INTRODUCTION

THAT diabetes mellitus is frequently associated with arteriosclerosis, and that the clinical consequences of the latter are the commonest causes of death in diabetes, are acknowledged. This association has led to the wide acceptance of the view that diabetes, by a hypothetic mechanism, is the cause of arteriosclerosis. This view is subject to a number of critiques:

1. The mere association of two disorders does not necessarily imply cause and effect, with the further implication that the diabetes comes first. The association may be interpreted reversely.

2. There is a regrettable diversity in definition of the term "arteriosclerosis."

3. In all studies of the incidence of arteriosclerosis in diabetes, only the arteries of the greater circulation have been studied, to the exclusion of the lesser.

4. It is assumed that diabetes is of unitary origin.

These critiques will be discussed in the course of our presentation.

No discussion of the relation of arteriosclerosis to diabetes can be logical without a definition of arteriosclerosis. Etymologically, any thickening or increased density of the arterial wall is "arteriosclerosis," but inasmuch as these properties comprise various structural alterations and mechanisms of their production, a differentiation of these various scleroses is essential. To date we recognize hyperplastic arteriosclerosis, atherosclerosis, Mönckeberg's sclerosis, thromboangiitis obliterans, infectious arteritis, periarteritis nodosa, and the arterial lesions of rheumatic fever. The morphology and pathogenesis of these varieties have been previously reviewed.[1] In order to arrive at a correct understanding of arteriosclerosis the problem must be viewed as a whole, not only from the standpoint of morphology but of physiology and, above all, dynamically. Only too frequently a part of the total summation of the lesions that represent arteriosclerosis has been deemed the essential lesion of arteriosclerosis. We refer particularly to lipoid infiltration; in consequence, the term " atherosclerosis" is often employed interchangeably with arteriosclerosis. In order to be valid as an entity, a lesion must be primary and must have a consistent background in morbid anatomy. True hyperplastic arteriosclerosis has such a background. We refer to the hyperplasia of the intima, of the elastica and of the media. Now these processes do not arise in adult life,

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but represent changes that begin at birth and proceed to old age. At birth the endothelial layer of the arteries lies directly upon the internal elastic membrane. Already in the first year an intima becomes visible between these layers and, as age advances, the intima progressively thickens by a growth of collagen until in old age it becomes fairly wide and is frequently either partially or completely hyalinized. Hyperplasia of the internal elastic lamina begins as early as the second year.[2] This begins in the larger arteries and involves the smaller vessels after middle life.[3] The media also increases in thickness. The following table from Schäfer [4] shows the measurements of the intima and of the media at different ages:

Age	Intima (microns)	Media (microns)
Birth	6	650
16 years	54	856
35 years	124	996
50 years	181	1,075
70 years	190	1,111

In other words, these hyperplastic processes represent a maturation of a normal evolutionary process, and it is therefore difficult to determine when physiologic aging ends and disease begins, since they merge so imperceptibly one into the other. Now this hyperplastic process may be considered the result of a compensatory mechanism, and the evidence is inescapable that this mechanism represents an adaptation to the progressive increase of intra-arterial tension from birth to old age, or, if there is no perceptible increase, to the prolonged maintenance of the normal pressure. If hypertension supervenes, these lesions occur earlier and are intensified. Hyperplastic arteriosclerosis is morphologically identical under both normotensive and hypertensive circumstances, except that the lesions are more severe in the latter.[5] We have already submitted much evidence showing that the normal intra-arterial pressure is the dominant factor in producing arteriosclerosis.[1] One of the principal evidences is the independence in incidence of gross arteriosclerosis of the pulmonary artery and of the aorta. Gross arteriosclerosis of the pulmonary artery practically never occurs unless sustained hypertension within the pulmonary artery can be predicated, and since the normal pressure in the pulmonary artery is only one-sixth that of the aorta,[6] and because even under maximum conditions obtaining in hypertension of the pulmonary artery the pressure never attains that of the normal intra-aortic pressure, the evidence is strong that the normal intra-arterial pressure, given sufficient time, can produce arteriosclerosis in the greater circulation—the decrescent arteriosclerosis of Allbutt. Another convincing evidence is obtained by observations on the morphologic analogue of hyperplastic arteriosclerosis in the veins, namely, phlebosclerosis. Phlebosclerosis never occurs unless a segment of the venous tree is subject to increased intravenous pressure.[1] Inasmuch as the normal pressure within the veins is low, a decrescent phlebosclerosis never occurs.

The following equation therefore appears applicable: arteriosclerosis = intravascular pressure × time.

If the causal relation between intra-arterial pressure and these hyperplastic processes is accepted, it becomes obvious why it is so difficult to demarcate where physiologic aging ends and arteriosclerosis begins. Jores,[7] an early and indefatigable student of arteriosclerosis, does not recognize arteriosclerosis until the hyperplastic changes are accompanied by lipoid infiltration; but inasmuch as the two lesions are so frequently independent and have different mechanisms, this viewpoint is hardly justified. We have employed as the criterion of hyperplastic arteriosclerosis that stage of the process when it becomes visible grossly. We feel that this distinction is justifiable since it serves as an accurate guide to the presence or absence of hypertension in areas of the vascular tree in which normally the pressures are much lower than in the aortic system. We refer to the pulmonary artery, the auricles and the venous system. Moreover, this criterion helps lessen the importance of the time factor, since gross arteriosclerosis is the earmark of juvenile hypertension. Finally, it helps to integrate the lesions and the mechanism of capillary sclerosis in the lungs, liver, kidneys, pancreas and spleen, which are observed only in association with gross arteriosclerosis or phlebosclerosis of the main supplying or efferent vessel of these organs.[8]

Our interpretation of the morphology and pathogenesis of hyperplastic arteriosclerosis is emphasized to distinguish it from atherosclerosis, which is the characteristic arterial lesion of diabetes mellitus. The morphology and pathogenesis of atherosclerosis are entirely different from those of hyperplastic arteriosclerosis. The reasons for regarding hyperplastic arteriosclerosis and atherosclerosis as separate entities have been previously summarized.[1] At best, atherosclerosis is a facultative but not an essential lesion of hyperplastic arteriosclerosis.

In view of the need of a fuller appraisal concerning the relation of arteriosclerosis to diabetes, it was decided to reopen the subject. For this purpose, 130 consecutive autopsies on cases of diabetes mellitus were studied. As controls, we selected within the same age group 103 consecutive autopsies on cases of essential hypertension, 66 cases of peptic ulcer, and 103 cases of carcinoma, almost entirely colonic.

We chose the cases of essential hypertension because of the close association between hypertension and diabetes.*

The following facts were determined: age; the presence or absence of arteriosclerosis in the aorta, the coronary arteries and the pulmonary artery; hypertension (over 150 systolic and 100 diastolic); the presence or absence of a lesion that could cause hypertension of the pulmonary circulation; the presence and morphology of lesions of the islands of Langerhans; the presence or absence of fibrosis of the pancreas; the presence and nature of arterial lesions within the pancreas, and the cause of death. In studying

*The variations in the number of cases in the tables are due to the incompleteness of the data in certain cases.

the lesions of the pancreatic arteries, a distinction was made between arteriosclerosis and hyalinization of the vessel wall, since we believe the latter is only a facultative lesion in arteriosclerosis. In a number of cases, serial sections of the pancreas were made.

It will be noted that the curves are fairly uniform. The differences in the four series of cases are the following: There were six deaths from diabetes below the age of 30. These may be regarded as instances of juvenile diabetes. There were only three deaths from essential hypertension below this age, and no deaths from peptic ulcer or carcinoma. The incidence of deaths from diabetes in the sixth and seventh decades is higher than in the other three groups. This incidence of death in diabetes accords with the statistics of Joslin.[9] In his series, the highest percentage of deaths was in

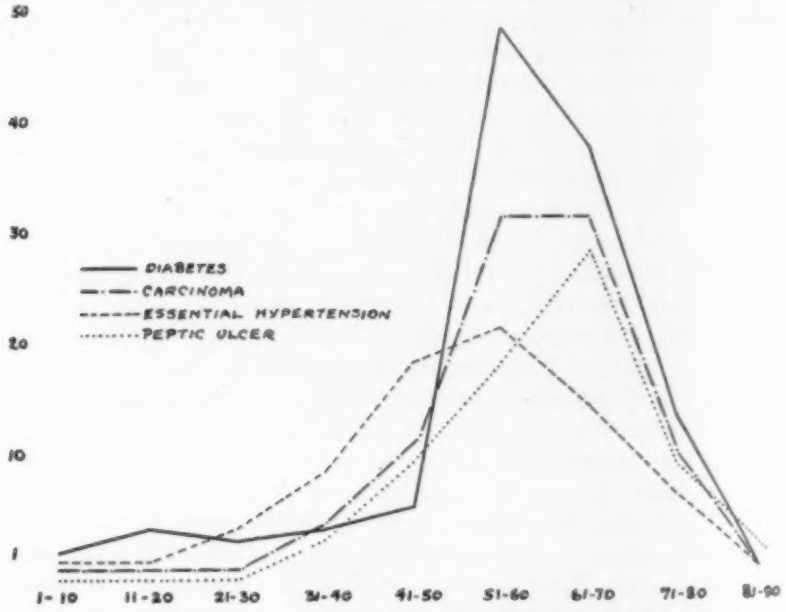

CHART 1. Age incidence by decades in deaths from diabetes, essential hypertension, peptic ulcer and carcinoma.

the seventh decade. The comparatively low curve in essential hypertension is to be expected from the prognostic significance of the malady. The average age in diabetes was 57.7 years; in essential hypertension, 54.3 years; in peptic ulcer, 59.3 years, and in carcinoma, 60.4 years.

The percentage of arteriosclerosis of the pulmonary artery in diabetes is identical with that in peptic ulcer and slightly higher than in carcinoma. The reason for the higher incidence in diabetes as compared to carcinoma is due both to the much higher rate of congestive failure in diabetes (16.1 per cent, as compared to 7.8 per cent), which accords with clinical experience, and to the somewhat higher per cent of emphysema (39.8 per cent, as com-

TABLE I

Incidence of Arteriosclerosis of Pulmonary Artery

	Total Cases	Cases and Per Cent Emphysema	Cases and Per Cent Emphysema and Congestive Failure	Cases and Per Cent Emphysema and Mitral Disease	Cases and Per Cent Emphysema and Pleural Adhesions	Cases and Per Cent Emphysema and Bronchiectasis	Cases and Per Cent Emphysema and Sarcoidosis	Cases and Per Cent Emphysema and Bronchial Asthma	Cases and Per Cent Emphysema and Kyphoscoliosis	Cases and Per Cent Emphysema and Fibrous Tuberculosis	Cases and Per Cent Congestive Failure	Cases and Per Cent Mitral Disease	Cases and Per Cent Tetralogy of Fallot	Data Insufficient	Cases and Per Cent Total Emphysema	Cases and Per Cent Total Congestive Failure	Cases and Per Cent Total Arteriosclerosis of Pulmonary Artery
Diabetes	130	27 20.8	3 2.3	2 1.5	7 5.5	1 0.8	1 0.8	—	—	—	18 13.8	5 3.8	1 0.8	—	41 39.8	21 16.1	65 50.0
Essential Hypertension	103	23 22.4	13 12.6	1 0.9	—	—	—	2 1.9	1 0.9	—	19 18.5	5 4.9	—	—	40 38.8	32 31.1	64 62.1
Peptic Ulcer	66	15 23.2	2 3.2	—	3 4.6	3 4.6		3 4.6	1 1.5	1 1.5	3 4.6	1 1.5	—	1 1.5	28.0 43.2	5 7.8	33 50.0
Carcinoma	102	22 21.6	2 1.9	2 1.9	6 5.9						6 5.9	6 3.9		1 0.9	32 31.2	8 7.8	43 42.0

pared to 31.3 per cent). The appreciably higher percentage of arteriosclerosis of the pulmonary artery in essential hypertension as compared to the other three groups is due entirely to the higher rate of congestive failure (31.1 per cent). It is evident that the main cause of the hypertension of the pulmonary circulation in these groups is emphysema, with congestive failure next in order. We do not intend to convey that emphysema is always followed by arteriosclerosis of the pulmonary artery. The duration is obviously of importance. As evidence, the right heart was enlarged and hypertrophied almost invariably in the cases in which the emphysema was accompanied by gross arteriosclerosis of the pulmonary artery, while in the presence of a normal pulmonary artery the protocols showed a normal right heart. The mechanism whereby emphysema causes hypertension of the pulmonary circulation and its natural history have been previously submitted.[1]

On the other hand, arteriosclerosis of the aorta and the coronary arteries occurred in all diabetics except six, all of whom were instances of juvenile diabetes. Two individuals were 32 and 37 years old, respectively; the remaining five varied in age between six and one-half and 20. In all of these the pulmonary artery also showed no gross arteriosclerosis.

These observations negate the contention that diabetes mellitus causes

TABLE II

Arterial Lesions in Pancreas According to Age

Age	Diabetes								Essential Hypertension							
	Total Cases	Cases and Per Cent Hyaline Arteries Alone	Cases and Per Cent Arteriosclerosis Alone	Cases and Per Cent Hyaline and Arteriosclerosis	Cases and Per Cent Total Hyaline Arteries	Cases and Per Cent Total Arteriosclerosis	Cases and Per Cent Total Arterial Lesions	Cases and Per Cent without Arterial Lesions	Total Cases	Cases and Per Cent Hyaline Arteries Alone	Cases and Per Cent Arteriosclerosis Alone	Cases and Per Cent Hyaline and Arteriosclerosis	Cases and Per Cent Total Hyaline	Cases and Per Cent Arteriosclerosis	Cases and Per Cent Total Arterial Lesions	Cases and Per Cent No Arterial Lesions
1–10	1	0 0	0 0	0 0	0 0	0 0	0 0	1 100.0	0	—	—	—	—	—	—	—
11–20	3	0 0	0 0	0 0	0 0	0 0	0 0	3 100.0	0	—	—	—	—	—	—	—
21–30	2	0 0	0 0	0 0	0 0	0 0	0 0	2 100.0	3	0 0	1 33.3	2 66.7	2 66.7	3 100.0	3 100.0	0 0
31–40	2	0 0	0 0	1 50.0	1 50.0	1 50.0	1 50.0	1 50.0	8	0 0	0 0	8 100.0	8 100.0	8 100.0	8 100.0	0 0
41–50	5	1 20.0	1 20.0	1 20.0	2 40.0	2 40.0	3 60.0	2 40.0	18	0 0	2 11.1	15 83.3	15 83.3	17 94.4	17 94.4	1 5.6
51–60	48	13 27.1	4 8.4	26 54.2	39 81.3	30 62.6	43 89.6	5 10.4	21	0 0	2 9.5	19 90.5	19 90.5	21 100	21 100.0	0 0
61–70	37	8 21.7	1 2.7	23 62.2	31 83.9	31 64.9	86.5	5 13.5	14	0 0	5.0 35.7	9 64.3	9 64.3	14 100	14 100.0	0 0
71–80	13	1 7.6	1 7.6	11 84.6	12 92.2	12 92.2	13 100.0	0 0	6	2 33.3	1 16.7	3 50.0	5 83.3	4 66.7	6 100.0	0 0
81–90	0	—	—	—	—	—	—	—	0	—	—	—	—	—	—	—

TABLE II—*Continued*

Arterial Lesions in Pancreas According to Age

Age	Peptic Ulcer								Carcinoma							
	Total Cases	Cases and Per Cent Hyaline Arteries Alone	Cases and Per Cent Arteriosclerosis Alone	Cases and Per Cent Hyaline and Arteriosclerosis	Cases and Per Cent Total Hyaline	Cases and Per Cent Total Arteriosclerosis	Cases and Per Cent Total Arterial Lesions	Cases and Per Cent No Arterial Lesions	Total Cases	Cases and Per Cent Hyaline Arteries Alone	Cases and Per Cent Arteriosclerosis Alone	Cases and Per Cent Hyaline and Arteriosclerosis	Cases and Per Cent Total Hyaline	Cases and Per Cent Total Arteriosclerosis	Cases and Per Cent Total Arterial Lesions	Cases and Per Cent No Arterial Lesions
1-10	0	—	—	—	—	—	—	—	0	—	—	—	—	—	—	—
11-20	0	—	—	—	—	—	—	—	0	—	—	—	—	—	—	—
21-30	0	—	—	—	—	—	—	—	0	—	—	—	—	—	—	—
31-40	2	0 0	0 0	0 0	0 0	0 0	0 0	2 100	3	0 0	0 0	0 0	0 0	0 0	0 0	3 100.0
41-50	9	0 0	1 11.1	0 0	0 0	1 11.1	1 11.1	8 88.9	11	1 9.1	2 18.2	2 18.2	3 27.3	4 36.3	5 45.4	6 54.6
51-60	18	4 22.2	1 5.5	5 27.8	9 50.0	6 33.3	10 55.6	8 44.4	31	4 12.9	4 12.9	10 32.3	14 45.2	14 45.2	18 58.1	13 41.9
61-70	27	3 11.1	4 14.8	9 33.3	12 44.4	13 48.1	18 66.7	9 33.3	31	6 19.4	5 16.1	8 25.8	14 45.2	13 41.9	19 61.3	12 38.7
71-80	9	0 0	2 22.2	6 66.7	6 66.7	8 88.9	8 88.9	1 11.2	10	0 100.0	2 20.0	4 40.0	4 40.0	6 60.0	6 60.0	4 40.0
81-90	1	0 0	0 0	1 100.0	1 100.0	1 100.0	1 100.0	0 0	0	—	—	—	—	—	—	—

hyperplastic arteriosclerosis in the sense that we have defined it, since, if so, it would involve the arteries of the greater circulation and the pulmonary artery simultaneously. Lack of susceptibility to the development of pulmonary arteriosclerosis in diabetes cannot be raised as an issue because the relation to hypertension of the pulmonary circulation is clearly manifest in all four groups of cases.

The incidence of arteriosclerosis of the arteries of the greater circulation was no higher in diabetes than in the three control series. In fact, arteriosclerosis of the aorta and coronary arteries was omnipresent in all four groups, with the exception of the juvenile cases of diabetes mentioned above, and in one case of essential hypertension in an individual aged 30. Even in this latter case, arteriosclerosis of the vessels of the pancreas was noted.

However, the relation between arteriosclerosis and diabetes cannot be solved by noting the incidence of arteriosclerosis in the pulmonary artery, the aorta and coronary arteries alone. Most significant is the observation of the incidence of arterial changes within the pancreas. This is shown in table 2.

In the six cases of juvenile diabetes there was not a single instance of arterial disease within the pancreas. In the other cases there was a pro-

gressive increase with age of both hyaline degeneration and arteriosclerosis. This was also manifest in the per cent of total arterial lesions. The same relationships are mirrored in the cases of ulcer and carcinoma. In essential hypertension the per cent of total arterial lesions is practically 100. In this series no autopsy on a case of essential hypertension was encountered below the age of 20.

This table confirms the previous statement that the incidence of arteriosclerosis in the greater circulation mounts progressively with age. It also reveals that the incidence of hyaline degeneration of the arteries also in-

TABLE III

Arterial Lesions in the Pancreas Below and After Age of 40

	Total Cases	Total Cases and Per Cent Hyaline Alone	Total Cases and Per Cent Arteriosclerosis Alone	Total Cases and Per Cent Hyaline and Arteriosclerosis	Cases and Per Cent Total Hyaline	Cases and Per Cent Total Arteriosclerosis	Cases and Per Cent No Arterial Lesions	Cases and Per Cent Total Arterial Lesions
Diabetes below 40 years	8	0 0	0 0	1 12.5	1 12.5	1 12.5	7 87.5	1 12.5
Diabetes after 40 years	103	23 22.3	7 6.8	61 59.3	84 81.5	68 66.0	12 11.6	91 88.4
Essential hypertension below 40 years	11	0 0	1 9.1	10 90.0	10 90.0	11 100.0	0 0	11 100.0
Essential hypertension after 40 years	59	2 3.5	10 16.9	46 77.9	48 81.3	56 94.8	1 1.7	62 98.3
Peptic ulcer below 40 years	2	0 0	0 0	0 0	0 0	0 0	2 100.0	0 0
Peptic ulcer after 40 years	64	7 10.9	8 12.5	21 35.9	28 46.8	29 48.4	26 40.7	38 59.3
Carcinoma below 40 years	3	0 0	0 0	0 0	0 0	0 0	3 100.0	0 0
Carcinoma after 40 years	83	11 13.3	13 15.8	24 28.6	35 42.3	37 44.4	35 42.3	48.0 57.7

creases with age, an observation that has been amply stressed before.[10, 11, 12]

The relation of arterial lesions to age is strikingly shown in table 3, where the lesions are tabulated for ages below and after 40.

It was necessary to find the total number and percentage of arterial lesions in the pancreas in all four groups. This is shown in table 4.

An inspection of this table shows that the per cent of total cases of hyaline and arteriosclerotic arteries and, therefore, the total per cent of all arterial lesions in peptic ulcer and carcinoma, are practically the same (57.6 per cent and 55 per cent, respectively), while in diabetes the hyaline vessels are about 30 per cent and the arteriosclerotic vessels 15 per cent higher than

in peptic ulcer and carcinoma. The total per cent of all affected arteries is therefore about 25 per cent higher than in peptic ulcer and carcinoma. The brunt of the increase is largely reflected in the appreciable increase of hyaline degeneration. It is evident, therefore, that diabetes is one of the factors commonly associated with hyalinization of the arteries, an observation that has been stressed by Bell.[13]

In essential hypertension there is, as is to be expected, a profound increase in the incidence of arteriosclerosis, since only one case in 70 did not reveal it. Moreover, there is an increase in the incidence of hyalinization: about 40 per cent higher than in peptic ulcer and carcinoma and about 6 per cent higher than in diabetes mellitus. It is apparent that hypertension tends to produce hyalinization, also a hitherto reported observation.[11, 12] A

TABLE IV

Arterial Lesions in Pancreas

	Total Number of Cases	Cases of Hyaline Alone and Per Cent	Cases of Arteriosclerosis Alone and Per Cent	Cases and Per Cent of Hyaline and Arteriosclerosis	Total Cases of Hyaline and Per Cent	Total Cases and Per Cent Arteriosclerosis	Total Cases and Per Cent Arterial Lesions	Total and Per Cent No Arterial Lesions
Diabetes	111	23 20.7	7 6.3	62 55.9	85 76.6	69 62.2	85.0 82.9	19 17.1
Essential hypertension	70	2 2.9	11 15.7	56 80.0	58 82.3	67 95.7	69 98.6	1 1.4
Peptic ulcer	66	7 10.6	8 12.1	23 34.9	30 45.5	31 47.0	38 57.6	28 42.4
Carcinoma	86	11 12.8	13 15.1	24 27.9	35 40.7	40 43.0	48 55.8	38 44.2

part of the increase of arterial hyalinization in diabetics is therefore ascribable to its frequent association with hypertension.

There is a regrettable paucity of studies on the incidence of arterial lesions of the pancreas in diabetes. Cecil[14] in 90 cases found arteriosclerosis in the pancreas in 80 per cent. In one-half, these vessels also showed hyalinization. He also found that the incidence increases with age, inasmuch as 40 per cent occurred between the ages of 20 and 30 years and 77 per cent between the ages of 30 and 40 years, and all but two showed arteriosclerosis after the fortieth year. Moritz and Oldt,[5] in a series of routine autopsies, found arteriosclerosis of the pancreas in 30 per cent between the ages of 31 and 45, rising to 55 per cent at the age of 61 and over. When hypertension was associated, the per cent was 73 between the ages of 31 and 45, and 87 per cent after the age of 61. Weichselbaum,[15] Herxheimer[16] and Seyfarth[40] found arteriosclerosis of the pancreatic vessels in diabetes "frequently." Root,[17] on the other hand, found arteriosclerosis of

the pancreatic arteries in diabetes in only 5 per cent. The reason for this marked discrepancy is not clear.

The substantial increase in total arteriosclerosis in diabetes over that in peptic ulcer and carcinoma seemed at first to support the view that diabetes caused arteriosclerosis, until the relation of the arterial lesions to hypertension in these disorders was also tabulated.

In the first place, the incidence of hypertension in diabetes is somewhat less than 50 per cent (45.5 per cent), but is appreciably higher than in peptic ulcer and carcinoma. In other statistics it varies from 39 per cent [18] to 54 per cent.[20] The cause for the higher incidence of hypertension in peptic

TABLE V

The Arterial Lesions in Pancreas in Relation to Hypertension

	Total Cases and Per Cent	Cases and Per Cent Hyaline Alone	Cases and Per Cent Arterio-sclerosis Alone	Cases and Per Cent Hyaline and Arterio-sclerosis	Cases and Per Cent Total Hyaline	Cases and Per Cent Total Arterio-sclerosis	Cases and Per Cent No Arterial Lesions	Cases and Per Cent Total Arterial Lesions
Diabetes with hypertension	45 45.5	4 8.9	4 8.9	36 80.0	40 88.8	40 88.8	1 2.2	44 97.8
Diabetes no hypertension	54 54.5	19 27.8	3 5.5	21 38.9	36 66.7	25 44.4	15 27.8	39 71.2
Essential hypertension	68 100.0	1 1.5	11 16.2	55 80.9	56 82.4	66 97.0	1 1.5	67 98.5
Peptic ulcer with hypertension	20 35.1	0 0	4 20.0	13 65.0	13 65.0	17 85.0	3 15.0	17 85.0
Peptic ulcer no hypertension	37 64.9	4 10.8	3 8.1	7 18.9	11 29.7	10 27.0	23 62.2	14 37.8
Carcinoma with hypertension	22 23.4	2 10.5	5 26.3	12 63.2	14 73.7	17 89.4	0 0	22 100.0
Carcinoma no hypertension	72 76.6	9 14.3	5 7.9	11 17.5	20 47.6	16 25.4	38 60.3	39.7

ulcer as compared to carcinoma is not pertinent to our thesis. When the incidence of the arterial lesions in diabetes is tabulated in relation to the presence or absence of hypertension, one notes, as one would expect, that the incidence of hyalinization is about 22 per cent higher and of arteriosclerosis 44 per cent higher in hypertensive diabetics than in normotensive diabetics, and that the total percentage of arterial lesions in diabetes with hypertension is 97.8 per cent, while in diabetes without hypertension it is 71.2 per cent. These data would at first blush suggest that diabetics are prone to hypertension and, in consequence, to arteriosclerosis. Under such circumstances it is of course assumed that the diabetes comes first. However, a common clinical experience, the significance of which escaped those who regard this sequence as the rule, does much to clarify this relationship.

It is a well known clinical fact that patients with prolonged essential hypertension ultimately develop hyperglycemia and eventually a typical glucose tolerance curve and diabetes.[20, 21, 22, 23, 24, 25, 26, 27] This does not occur in youthful hypertensives. Herrick [25] many years ago deemed these cases a clinical syndrome. Such patients are always in the older age group, obese and neglectful in their eating habits. In the early stage, a reducing diet usually reduces the hyperglycemia and hypertension to normal or nearly normal levels and the hyperglycemia disappears. In the later phases, this consummation is no longer attained. The per cent of patients with essential hypertension who develop hyperglycemia varies with different observers. Maranon found this sequence in 55 per cent of hypertensives but according to most other observers it occurs in about 30 per cent. The incidence of glycosuria in hypertensives varies between 19 per cent and 36 per cent. Indeed, as O'Hare [22] remarked, one may regard every patient with essential hypertension as a potential diabetic. Maranon describes three stages: (1) hypertension with hyperglycemia; (2) hypertension with intermittent glycosuria, and (3) hypertension with persistent diabetes. The mechanism of the production of hyperglycemia in diabetes has been much debated. We shall reserve our view for later discussion.

There are a number of reasons why these cases of diabetes following hypertensive disease are often overlooked: (1) The glucose tolerance test is not done with sufficient frequency in hypertensive disease. (2) The renal threshold for glucose has been raised by the hypertension and an attendant renal insufficiency. (3) An anti-obesity diet lowers the hyperglycemia and may eliminate the glycosuria. (4) Death comes from a complication directly connected with the hypertension (coronary disease, apoplexy, renal insufficiency) before the diabetes becomes manifest. Here again, as in so many disorders, the problem requires attack from the biologic point of view. Statistics on the mutual relations between diabetes and essential hypertension lose most of their value unless we know which comes first.

Indeed, age without the intermediacy of hypertension may cause not only hyperglycemia but a typical diabetic glucose tolerance curve.[28, 29, 30] Marshall [30] found this to occur in 14 per cent of a group of men past the age of 65.

In summary, a considerable proportion of elderly diabetics have had antecedent essential hypertension, and this accounts for the increase in arteriosclerosis in diabetes above and beyond that consequent to senescence. We tried to discover how often our cases of diabetes were preceded by essential hypertension, and vice versa, but owing to the indeterminate onset of this disease and lack of knowledge on the patient's part we obtained too few figures to permit presentation.

There is no evidence that diabetes in adults promotes hypertension above and beyond that incident to age.[31, 32] It remains now to demonstrate the

relation of these arterial changes to the most conspicuous lesions found in diabetes, namely, the lesions in the islands of Langerhans.

Our per cent (47.3) of island lesions in diabetes accords with that of most observers.[37, 38, 39, 40, 41, 42]

The comparatively high percentage (11.4) of island lesions in essential hypertension is significant and not surprising, in view of the frequency of hyperglycemia in this disorder. Of the eight cases of essential hypertension in which island lesions were found, all but one were females. Three showed hyaline islands, two fibrosis, and three both fibrosis and hyaline. The youngest was aged 46, the oldest 71. Only one case showed a trace

TABLE VI

Incidence of Island Lesions* in Diabetes, Essential Hypertension, Peptic Ulcer and Carcinoma

	Total Cases	Total and Per Cent Island Lesion	Total and Per Cent Fibrosis of Islands	Total and Per Cent Hyaline Islands	Total and Per Cent Fibrosis of Hyaline Islands	Total and Per Cent Normal Islands
Diabetes	112	52 47.3	28 25.0	15 13.4	10 8.9	59 52.7
Essential hypertension	70	8 11.4	3 4.3	4 5.7	1 1.4	62 88.6
Peptic ulcer	66	0 0	0 0	0 0	0 0	0 0
Carcinoma	86	2 2.3	2 2.3	0 0	0 0	84 97.7

* Hydropic degeneration of the islands has been omitted for two reasons. First, in experimental diabetes in dogs it has proved to be reversible by administering insulin,[33] and is therefore a result and not a cause. Hydropic degeneration is usually found only in cases of diabetes that have been uncontrolled before death, and is in all probability the result of "overstrain" of the islands, a suggestion first made by Allen.[34] Second, it is closely simulated by postmortem change, to which the pancreas is notoriously susceptible.

We have also not stained for amyloid, except in a few cases. While some observers [35, 36] have found that a considerable per cent of the islands give this reaction, it is questionable whether these represent real amyloid, since in true general amyloidosis the islands do not show this reaction. We have not encountered a single instance of lymphocytic infiltration of the islands. According to all observers it is exceedingly rare.

of glycosuria during life. One individual died before a specimen of urine could be examined. In four, the blood glucose was measured; one showed 85, one 100, one 125, and one 156 mg. per cent. It is apparent that in only one case could diabetes have been suspected. In none was the number of affected islands more than minimal, so that it may be presumed that the amount of damage to the islands was not sufficient to produce a hypoinsulinemia.

No island lesions were found in the 66 cases of peptic ulcer. Two of 86 cases of carcinoma, or 2.3 per cent, showed fibrotic and hyaline islands. In neither of these was glycosuria present. In one the blood glucose was found to be 85 mg. per cent.

Obviously, whether these patients would ultimately have developed diabetes can no longer be determined.

Changes in the islands of Langerhans in nondiabetics have been previously described,[43, 17, 41, 42] but without any consistent clinical relationship except that they always occur in older individuals.

It appears that fibrosis and/or hyalinization of the islands is not confined to cases of diabetes, and that the absence of such lesions therefore cannot be utilized as a postmortem evidence that diabetes was not present. Nevertheless, the per cent of affected islands in diabetes is so large that it must bear a significant relation to the genesis of the disease.

The per cent of fibrous as compared to hyaline islands is not of much importance. It is the involvement and not the character that is of moment. The per cent of fibrous as compared to hyaline islands in diabetes varies widely with different observers, which is not surprising considering the difficulty in interpreting whether an island is fibrous or not. In examining many hundreds of islands from birth to old age, we have noted that as a rule the amount of fibrous tissue within the island increases with age. In infancy, the only connective tissue visible is the exceedingly thin basement membrane of the capillary walls. With maturity this wall slowly thickens, until in the seventh decade it becomes fairly prominent. Furthermore, as we shall demonstrate, this thickening of the capillary wall becomes much intensified under the influence of an associated hypertension. It is therefore difficult to determine where normality ends and where fibrosis begins. Arbitrarily we regard a fibrous island as one in which half or more of the surface area is occupied by fibrous strands.

We believe with Weichselbaum[15] that the fibrosis and the hyaline degeneration are not separate processes but that the fibrosis precedes the hyaline change, and for these reasons: (1) It is well established that hyaline material is deposited in inert fibrous tissue, for instance, in old scars, corpora lutea, healed tubercles, etc. (2) The two processes are very frequently associated in the same island and in the same pancreas. (3) In diabetes associated with hypertension, the lesions are predominantly fibrous. At this point it is necessary to add that in not a single instance has a round celled inflammatory reaction within an island been found, so that the fibrosis cannot be regarded as inflammatory. As we shall later try to show, it is the result of a progressive capillary sclerosis. All are agreed that the number of involved islands is not a measure of the severity of the diabetes but of its duration. They are therefore found almost exclusively in older diabetics.

The fact that over half of the pancreases in diabetes do not show island lesions is disappointing in respect to an exclusive anatomic basis for the pancreatic origin of diabetes. However, this does not exclude the possibility that in the pancreases that are anatomically intact, at least with our present methods, the islands may be functionally insufficient. This has many analogues in human disorders, for instance, in certain renal diseases.

Furthermore, one must appreciate that we are confronted with a biologic process. Because death has occurred is no warrant for believing that we are witnessing an end result in the sense of morbid anatomy. These statistics may only be viewed as representing phases of a protracted process which undoubtedly would have progressed had not death intervened, and particularly in this disorder, in which death comes sometimes prematurely not so much from the diabetes (coma), but from a cardiovascular complication.

TABLE VII

Relation of Age to Island Lesions

Age	Diabetes		Essential Hypertension		Peptic Ulcer		Carcinoma	
	Total Cases	Total Island Lesions and Per Cent	Total Cases	Total Island Lesions and Per Cent	Total Cases	Total Island Lesions and Per Cent	Total Cases	Total Island Lesions and Per Cent
1–10	1	0	0	—	0	—	0	—
11–20	3	0	0	—	0	—	0	—
21–30	2	1 50.0	3	0	0	—	0	—
31–40	2	0 0	8	0	2	0 0	3	0 0
41–50	5	3 60.0	18	3 16.7	9	0 0	11	0 0
51–60	48	24 50.0	21	1 4.8	18	0 0	31	0 0
61–70	37	15 40.6	14	3 21.4	27	0 0	31	2 6.5
71–80	13	6 46.2	6	1 16.7	9	0 0	10	0 0
81–90	0	—	0	—	1	0 0	0	—
Total	111	49 44.1	70	8 11.4	66	0 0	86	2 2.3

In order to determine the relation of these island lesions to diabetes, it is essential to obtain further data; and in particular their incidence in respect to age.

There was not a single instance of either fibrosis or hyalinization of an island in diabetes below the age of 20, and only one in the third decade, a male of 29 with a diabetes of unknown duration, who died from a malignant teratoma of the testis with metastases. The others in this age group all died in diabetic coma. Of eight cases of diabetes, who died below the age of 40, only one showed an island lesion and this was of the fibrous type. This is identical with the experience of all students of the morbid anatomy of the islands in youth.[44, 45, 46, 39, 40, 16, 14] This observation in connection

with the different clinical behavior and course of juvenile diabetes makes one suspect that the diabetes of childhood has a different origin from that occurring in the mature years. Juvenile diabetes is more severe, the glucose tolerance is less, it is more subject to coma, insulin control is more difficult, and the hereditary tendency is greater.[45]

From our table it is clear that there is a sudden rise in the incidence of island lesions after the fortieth year, not only in diabetes but in essential hypertension. The two island lesions of the 86 carcinoma cases also occurred in the seventh decade. There is no progressive rise in the per cent of island lesions according to decades, but the number of cases is too few to be decisive.

Apparently some unknown factor must become operative after the fifth decade that causes this abrupt rise in the incidence of island lesions. The

TABLE VIII

Relation of Hypertension to Island Lesions, in Diabetes, Essential Hypertension, Peptic Ulcer and Carcinoma

	Total Cases	Total Cases and Per Cent Island Lesions
Diabetes with hypertension	45	26 57.7
Diabetes without hypertension	58	17 29.3
Essential hypertension	70	8 11.3
Peptic ulcer with hypertension	20	0 0
Carcinoma with hypertension	22	1 4.5
Carcinoma without hypertension	72	1 1.4

comparatively high incidence of island lesions in essential hypertension might furnish a clue to the nature of this factor, for the reason that hypertension increases the incidence of hyperplastic arteriosclerosis.

The one significant fact in this table is the profound increase in island lesions in diabetes associated with hypertension as compared to diabetes with normal intravascular pressure (57.7 per cent as compared to 29.3 per cent). This significant increase made it necessary to determine the relation of the arterial lesions in the pancreas to the island lesion.

Here one notes the remarkable fact that, when island lesions are found in the pancreas in diabetes, lesions of the arteries are practically always encountered. In only one of 52 cases with island lesions (or 1.9 per cent) were no arterial lesions found. While the hyaline islands were slightly more frequently associated with hyalinization of the arteries than with arteriosclerosis, the difference was not great enough to be significant.

TABLE IX

Relation of Islet Lesions to Arterial Lesions in Diabetes

	Total Island Lesions	Per Cent Hyaline Arterioles Alone	Per Cent Arteriosclerosis Alone	Per Cent Hyaline and Arteriosclerosis	Per Cent Total Hyaline Arterioles	Per Cent Total Arteriosclerosis	No Arterial Lesions	Total Arterial Lesions
Hyaline islets	15	46.7	13.3	40.0	86.7	53.3	0	100.0
Fibrosis of islets	27	10.3	14.3	71.4	81.7	85.7	4.0	96.0
Fibrosis and hyaline islets	10	10.0	10.0	80.0	90.0	90.0	0	100.0

Only one case, or 1.9 per cent of total island lesions, was unassociated with arterial lesions.

The same invariable association between island lesions and arterial lesions was found in the eight cases of essential hypertension without clinical diabetes.

Cecil [14] found that, of the 61 cases of hyalinization and fibrosis of the islands, all but five were associated with arteriosclerosis.

What is the significance of the almost invariable association between the island lesions and the arterial lesions? The island lesions are not inflammatory in origin. A hypothetic toxic substance has been invoked, but it is difficult to conceive how a toxic substance over a prolonged period would often not injure a pancreas at all and at other times do so in such an unpredictable and haphazard manner. Hyperglycemia cannot be the cause, because all the islands would be affected.

It has been suggested that the island changes may represent a simultaneous reaction with or an extension from the interacinous fibrosis that is unusually common in diabetes. Our own studies show that the island changes occur almost as often in the intact organ as in that severely fibrotic. It is well known that, in profound interacinous fibrosis due to pancreatic lithiasis, the islands are nearly always intact. The only reasonable explanation is that the vascular lesions must affect the island lesions either directly or indirectly. The answer lies in the morphogenesis of these fibrous and hyaline islands. All [36, 37, 17, 57, 14, 43, 15] are agreed that the hyaline deposits and fibrosis are always pericapillary. The hyalin is only rarely within the

TABLE X

Relation of Islet Lesions to Arterial Lesions in Essential Hypertension without Clinical Diabetes

	Total Island Lesions	Per Cent Hyaline Arterioles Alone	Per Cent Arteriosclerosis Alone	Per Cent Hyaline and Arteriosclerosis	Per Cent Total Hyaline	Per Cent Total Arteriosclerosis	No Arterial Lesions	Total Arterial Lesions
Hyaline islets	4	25.0	0	75.0	100.0	75.0	0	100.0
Fibrosis of islets	3	0	0	100.0	100.0	100.0	0	100.0
Fibrosis and hyaline islets	1	0	100.0	0	0	100.0	0	100.0

epithelial cells of the island. It is situated in the wall of the capillary external to the endothelial layer, between the capillary basement membrane and the epithelial cells of the island itself. This appearance is especially clear in the early phase (figure 1). In the later phases, the hyaline deposit widens and, expanding outwardly, compresses the adjacent epithelial cells until ultimately they completely disappear (figures 2 and 3). At the same

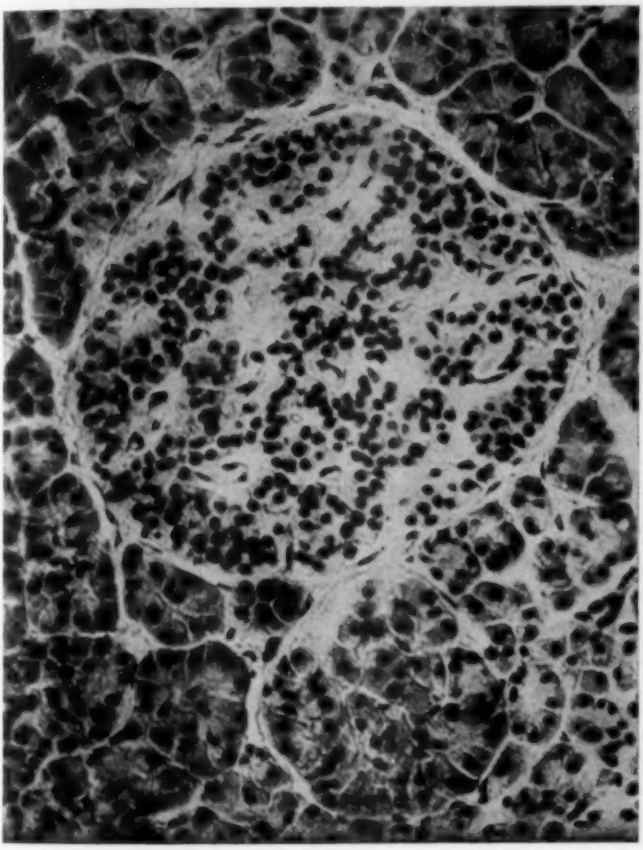

FIG. 1. Beginning hyalinization of an island of Langerhans, showing thickened intima of capillaries by the hyaline deposit beneath endothelial lining.

time the capillary lumen becomes progressively narrowed until the walls come into contact and the capillary lumen is represented only by strands of the much compressed endothelial cells. The fibrous islands which represent the preceding phase of hyalinization are the result of a progressive thickening of the basement membrane of the capillaries, and no matter how extensive the thickening, the capillary lumen is compressed but never completely obliterated (figure 4). With higher magnifications, the hyaline deposits

reveal a fibrillary structure outlining the erstwhile fibrous strands. The thickening of the intima of the capillaries is consistent with the biologic interpretation of arteriosclerosis, as previously set forth.

In this interpretation, the fibrous and hyaline islands represent areas of capillary sclerosis, identical in morphology to that we have described in the pulmonary alveoli in hypertension of the pulmonary circulation with

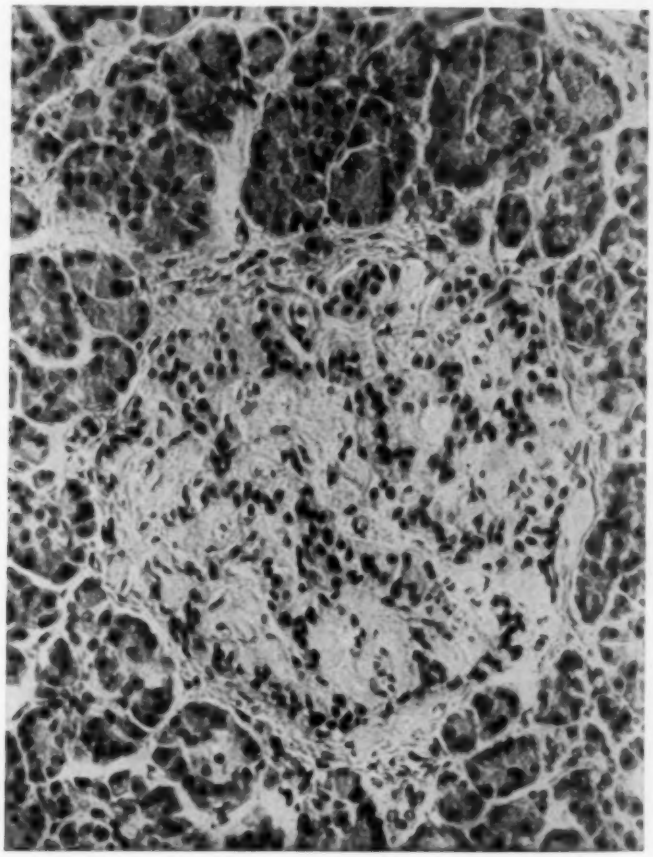

FIG. 2. More advanced stages of hyalinization of an island of Langerhans, showing compressed island cells.

arteriosclerosis of the pulmonary artery,[47] in the glomeruli in hypertension of the greater circulation with arteriosclerosis of the renal artery [1] and in the hepatic sinusoids in cardiac cirrhosis, and with phlebosclerosis of the hepatic veins.[48] The subject of capillary sclerosis from an anatomic and functional viewpoint has recently been reviewed.[8] The terms "arterio-capillary" or "venocapillary" sclerosis are applicable to such lesions. Indeed Weichselbaum [15] many years ago regarded the island lesions in diabetes as

representing a capillary sclerosis, but suggested no explanation for this phenomenon. Herxheimer [16] termed the summation of the process as "pancreato-cirrhosis arteriosclerotica."

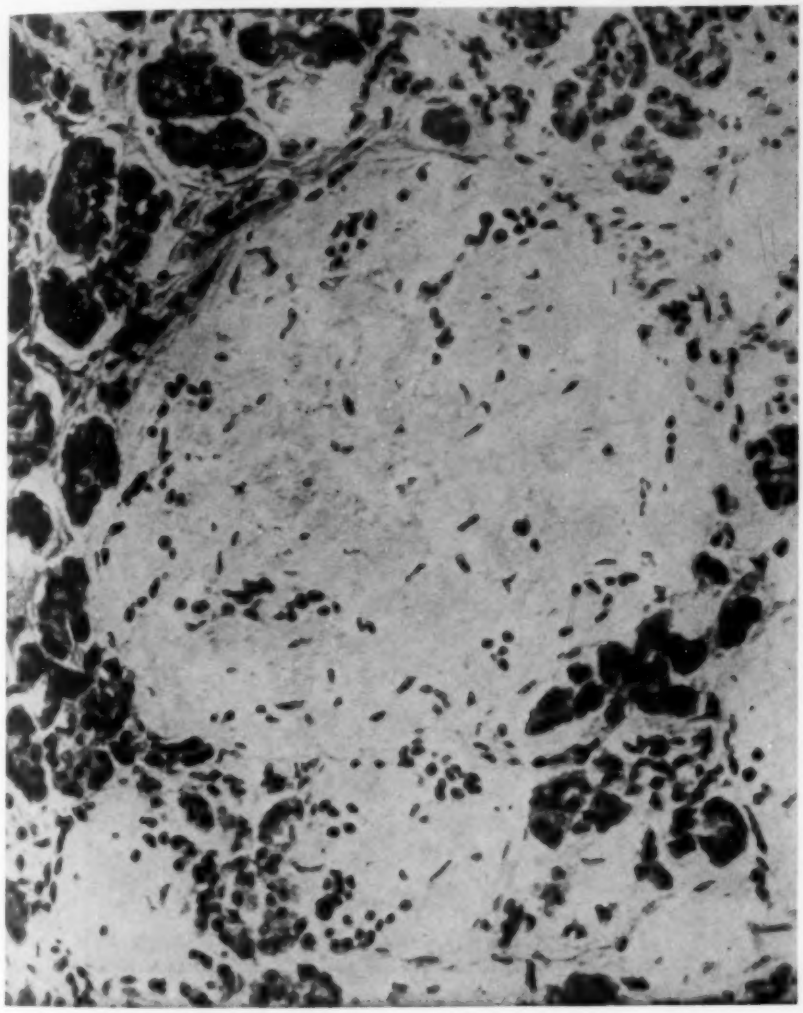

FIG. 3. Advanced stage of hyalinization of island of Langerhans, showing a few compressed island cells and almost obliterated capillaries with distorted and compressed endothelial lining.

The explanation for the mechanism whereby sclerosis of the capillaries is produced is two-fold: (1) by direct extension of the hyaline involvement of the afferent arteriole into the capillaries, sometimes visible in serial sections, as in figure 5; (2) by interference with the circulation of the island. These mechanisms are precisely those observed in the glomerulus in older

individuals with generalized arteriosclerosis and especially if associated with hypertension. Jaffe [49] has shown by serial section of such glomeruli that the hyalinization does not always arise from a direct extension of the hyalinized afferent arteriole but is sometimes disconnected.

The tendency for hyalinization in diabetes is not limited to the capillaries and arteries of the pancreas. In studying the sections of the kidney simultaneously, it was noted that when the arterioles of the pancreas were

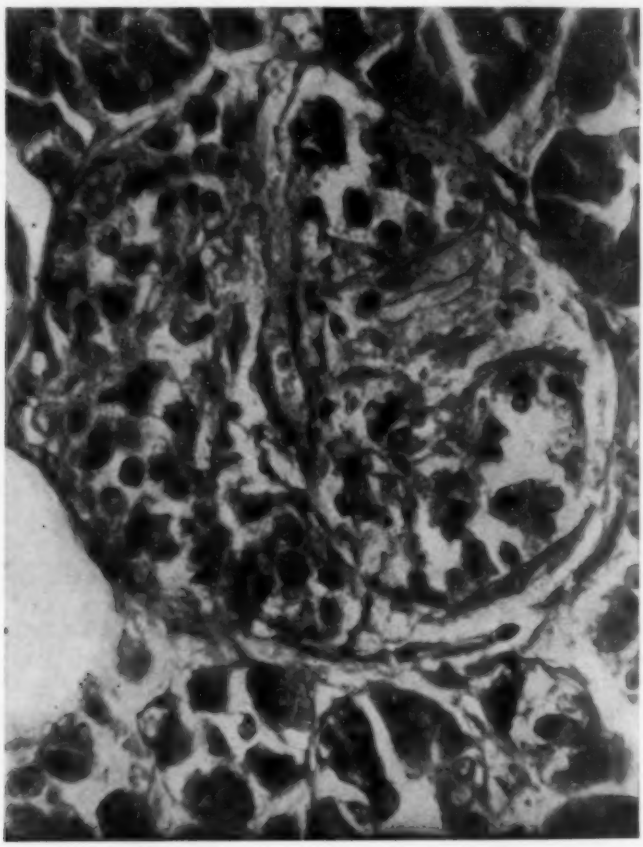

FIG. 4. Fibrosis of island of Langerhans, showing thickened capillaries.

hyalinized those of the kidney were also affected but to a greater degree, an observation confirmed by Aschoff.[50] At the same time, when there were no island lesions, the glomeruli were intact or only slightly involved.

The question now arises: Why is the capillary sclerosis so less widespread in the pancreas than in the kidney; in other words, why are the islands affected in about half of the total number of diabetics, while in the kidney the glomeruli are affected in practically 100 per cent? We believe

the answer lies in the different circulations in the two organs. The kidney is supplied by one vessel and the only anastomoses are with trivial vessels entering the capsule. The kidney is therefore an end organ, and thus particularly subject to infarction. Furthermore, the capillaries of the glomerular tufts do not anastomose with the parenchymal capillaries. On the other hand, the pancreas is supplied by three arteries. The head of the pancreas is supplied by the superior pancreaticoduodenal and the inferior

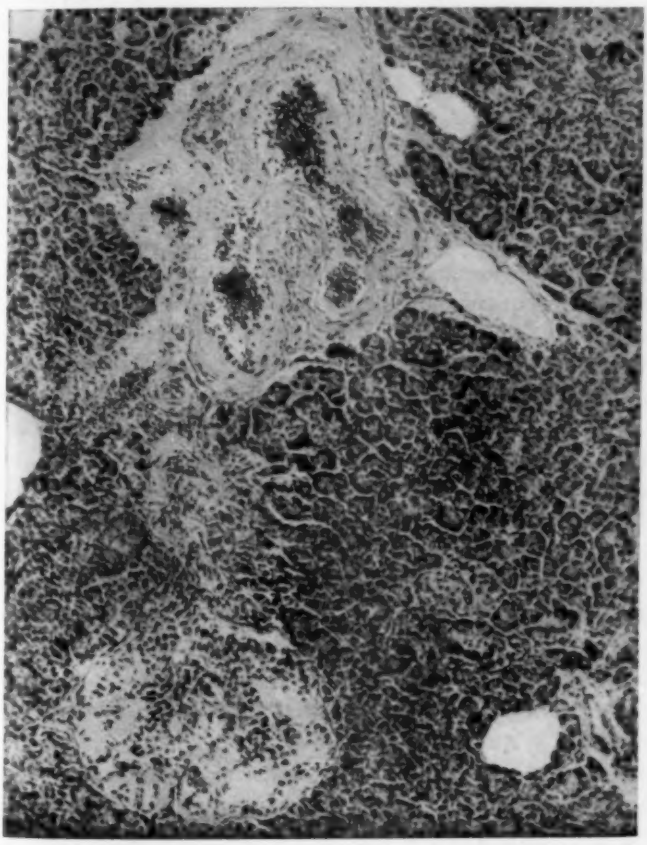

FIG. 5. A hyalinized island of Langerhans continuous with a hyalinized afferent arteriole.

pancreaticoduodenal arteries, while the tail is supplied by branches of the splenic artery. Moreover, these anastomose freely within the organ. The circulatory pattern of the islands mirrors that of the gross blood supply. According to Beck and Berg[51]: "The afferent arterioles are short and slightly larger than the capillaries. They arise from the intralobular arteries. The number varies with the size of the islands. In the larger ones two or more afferent arterioles may be present." In describing the capillary network of the islands they say: "At frequent intervals short twigs are given off

forming intercommunications between the loops. Rich anastomoses are found to exist between the capillaries of the islands and the interacinar rete. . . . More than one efferent venule is usually present, depending on the size of the islands. These empty into the interlobular veins. They usually follow the surface of the island for a short distance, receiving numerous tributaries from the insular capillaries along their course. In addition efferent venules receive tributaries from the adjacent interacinar capillaries. *When thrombosis, embolism, sclerosis or spasm of the afferent arterioles occur, the capillary anastomosis can form a collateral circulation which maintains an adequate blood supply to the islands. This mechanism accounts for the few changes which are observed in the islands in the presence of arteriolar lesions.*" (*Italics mine.*) The infrequency of infarction in the pancreas is recognized.

If in the adult type of diabetes the islands are diseased in only half the cases, how are we to account for the hypoinsulinemia in the other intact half? We submit the explanation that the islet function has been so disturbed by the impairment of blood supply from the disease of the afferent arteriole, with consequent narrowing, that the production of insulin becomes insufficient. This mechanism has other analogues in the disease, notably in the kidney. It is well known that renal insufficiency may occur with morphologically intact kidneys, in shock, dehydration, myocardial failure, etc. Insufficiency of the heart, the lungs and the liver can arise even if the arteries are intact. That arterial disease may depress the production of insulin without anatomic damage to the islands has been previously suggested.[23, 52, 20]

The proposition that diabetes in persons over 40 frequently arises from arteriosclerosis has been broached often enough,[26, 40, 53, 39, 16, 20, 18, 54, 52] but has not attained a wide foothold. The argument has been raised that arteriosclerosis cannot be the cause of diabetes because the incidence of diabetes lessens and the malady improves with age, while the arteriosclerosis presumably progresses. Even granting that such is the case (although it is by no means always true), it is well to recall that diabetes is not a static condition and is modified by many extrapancreatic factors, for instance, the basal metabolic rate and state of nutrition and exercise. Older people tend to lose weight, which lowers the blood pressure and thus affects the hyperglycemia. By the same token, hypertension has a slower tempo in older persons than in younger, although the arteriosclerosis increases. The lowered incidence of diabetes in old age [17] is probably due to the circumstance that death has occurred before the diabetes is clinically manifest. We have already referred to the fact that hyperglycemia is very common in old age, even without hypertension.

It remains to account for the greater incidence of gangrene in diabetes, and the observation that juvenile diabetes is frequently followed by vascular disease. All observers agree that the type of arteriosclerosis is the

same in both diabetics and nondiabetics except in one particular, namely, the unusual quantity of atheroma.[17, 37, 55, 44, 56] The atherosclerosis is no doubt the result of the hyperlipemia and, more particularly, hypercholesteremia so common in diabetes uncontrolled with insulin.[37, 17, 58, 55] A hypercholesteremia is not even essential, provided there is an associated hypertension which initiates an increased permeability of the vessel wall.[59] Lehnherr [56] found the lipoid content of the aorta higher in diabetics than in nondiabetics and, in terms of cholesterol, 8.07 gm. per cent as compared to 4.8 gm. per cent. A hypercholesteremia is usually well controlled with an adequate administration of insulin. Lawrence [60] and Boyd and his coworkers [61] report their observations on children institutionalized for diabetes: after 10 years or more of the closest supervision of their diet, and with insulin control, only two showed vascular change, one a girl of 20 who had had diabetes since the age of two, the other who had a beginning retinitis.

On the other hand, Dolger [62] found that all juvenile diabetics developed vascular lesions "regardless of the age of onset, the severity of the diabetes or type of treatment used. Retinopathy usually presaged progressive vascular degeneration. Fifty per cent of patients exhibited hypertension and albuminuria at the time of earliest retinal hemorrhage." Whether these vascular changes are associated with hyperplastic arteriosclerosis or atherosclerosis has not been demonstrated.

In atherosclerosis, the greatest deposition of the lipoids is in the intima, where these accumulations bulge into the lumen and thus tend to occlude the vessel. This accounts, in all probability, for the higher incidence of gangrene in diabetics than in nondiabetics.

Hyperlipemia and hypercholesteremia bear no consistent relation to hyperplastic arteriosclerosis.[63]

Summary

The term "arteriosclerosis" demands a stricter definition than is currently in vogue, and should be limited to that variety characterized by simultaneous hyperplasia of the intima, elastica interna and of the media. *Athero*sclerosis must be sharply distinguished from *arterio*sclerosis. Gross arteriosclerosis of the aorta and of the pulmonary artery are entirely independent. Gross arteriosclerosis of the pulmonary artery occurs no more frequently in diabetes than in controls within the same age group. This observation excludes the possibility that diabetes causes hyperplastic arteriosclerosis. The incidence of arteriosclerosis of the aorta and of the coronary artery was no higher in diabetics than in the control groups. There is a substantial increase above that consequent to senescence in the incidence of arterial lesions in the pancreas in diabetes as compared to control groups. The brunt of this increase is largely dependent on the increase of hyalinization. The increase in hyalinization is the result partly of the diabetes itself and partly of an associated hypertension. Hypertension appreciably in-

creases the total incidence of arterial lesions in the pancreas as compared to normotension.

The apparent increase of arterial changes in the pancreatic arteries in diabetes is only specious and is explainable by the clinical observation that older individuals with prolonged essential hypertension are potential diabetics; therefore, the number of older diabetics in whom the hypertension precedes the diabetes is considerable. Advanced age, even without hypertension, may produce hyperglycemia and diabetes. Hyalinization and fibrosis of the islands of Langerhans occur in about one-half of the pancreases of the older diabetics, but rarely in children. These lesions are therefore not specific lesions of diabetes. The arteries of the pancreas were involved in practically 100 per cent of cases in which island lesions were present. The island lesions are interpreted morphogenetically as a capillary sclerosis, precisely comparable to that found in alveolar capillaries of the lung, the sinusoids of the liver, and in the glomeruli in the presence of arteriosclerosis and phlebosclerosis affecting the main vessels of these organs. The capillary sclerosis is either the result of the extension of the fibrosing or hyalinizing lesion of the afferent arteriole of the island into the capillaries, or of diminution of the blood supply. The reason why island lesions do not occur more frequently in diabetes is the special pattern of blood supply in the pancreas. The cause of the hypoinsulinemia in the cases in which the islands are intact is a functional insufficiency, consequent to the impairment of the blood supply to the islands. The higher incidence of gangrene of the lower extremity as compared to nondiabetics is viewed as the result of atherosclerosis, which is the characteristic lesion of diabetes. The atherosclerosis is due to a hyperlipemia and, more particularly, hypercholesteremia. This is also the cause of the frequent atherosclerosis found in juvenile diabetics. Inasmuch as diabetes in juveniles is clinically different from that in adults, and island changes are usually absent in juveniles, there is reason to suspect that the disease has a different origin from that in adults. All the submitted evidence makes it fairly certain that in older individuals hyperplastic arteriosclerosis precedes but does not follow the diabetes.

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CHRONIC TRENCH FOOT: A STUDY OF 100 CASES *

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INTRODUCTION

TRENCH (immersion) foot may be considered a form of frostbite, i.e., a response of living tissues to injury by cold. Understanding of the basic changes taking place in the acute phase of trench foot, and the logical conclusions as to treatment of this phase, have been greatly clarified by excellent bulletins from the Surgeon General's Office and by the work of White,[1] Ungley and Blackwood,[2] Lange, Weiner and Boyd [3] and others. Silverman [4] has given an interesting report on cases of subacute trench foot. Except for experimental work by Burch and associates,[5] and a preliminary report by one of us,[6] we know of no comprehensive study on the late, chronic phase of trench foot.

This study obviously could not determine what proportion of cases of acute trench foot finally pass into the chronic phase. It can serve merely to describe the clinical picture and to try to explain the symptomatology.

MATERIALS AND METHODS

One hundred cases of trench foot without other disease were used. A detailed history and physical examination of each case were recorded on a "vascular chart." All the patients had gone through the acute phase of trench foot during the winter of 1944–1945 in the European campaign. In all of them the acute phase had gradually passed into that chronic disability which is the subject of this study.

The cases were placed on the following regimen for peripheral vascular care:

1. Complete abstinence from tobacco.
2. Two to three ounces of whiskey or three glasses of wine daily.
3. Daily Buerger's exercises for a half hour twice a day.
4. Foot care, including a daily foot bath and application of lanolin; proper shoes, changing of socks, etc.
5. Social adjustment where indicated.
6. Treatment of epidermophytosis.

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The work tolerance was measured while the patients were engaged in their normal occupations and was expressed in degree of endurance to prolonged walking and standing. Quantitative ergographic studies will be reported elsewhere. The patients were observed at frequent intervals and changes were recorded on the chart.

TABLE I

Sensitivity to Temperature and Humidity

	Mild	Moderate	Severe
Sensitivity to cold	—	—	100
Sensitivity to heat	76	24	—
Sensitivity to dampness	—	100	—

The responses to change in temperature and humidity expressed in degree of pain and work tolerance were recorded throughout the year.

FINDINGS

All of our patients had difficulty in adjusting to temperature changes; all of them were markedly sensitive to cold (table 1). Ninety-one out of the 100 patients gave a definite history of pain on walking; 32 stated that walking two to four blocks caused pain. These 91 patients also complained of pain on prolonged standing; 72 of the group reported color changes (table 2). Objectively, the figures for abnormal postural changes came close to the figures of subjective complaints (tables 3 and 4), even if only severe

TABLE II

Symptoms and Signs Reported by 100 Patients

Symptoms	Mild	Moderate	Severe	Total
Pain on walking	12	47	32	91
Pain at rest	19	9	4	32
Coldness	6	40	52	98
Cyanosis	7	39	8	54
Pallor	3	22	11	36
Rubor	8	9	1	18
Numbness	9	58	26	93
Tingling	12	58	26	96
Burning	10	56	26	92
Anesthesia	1	1	1	3
Stiffness	5	8	3	16
Excessive sweating	6	33	49	88
Edema	38	41	3	82
Infection	5	1	—	6*
Ulcers	2	1	—	3†
Gangrene	2	—	—	2‡
Phlebitis	2	—	—	2

* Both feet, cellulitis incised and drained.
† One, middle toe right foot; 1, both feet.
‡ One, amputation all toes both feet; 1, amputation all toes of right foot.

TABLE III

Site and Degree of Color Changes at Rest

Site*	Cyanosis			Rubor			Pallor		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Fingers		1							
Hand		1		1					
Toes	27	29	14	3	5	1	2		1
Mid-foot	23	22	1	2	2	1	4	1	
Plantar	5	18	3	2	1	1	1	6	1
Ankle	3	2							

* No cyanosis, rubor or pallor in wrist, forearm, arm or leg.

reactions (3 and 4 plus) are included. The procedures used to elicit changes due to posture were:

1. The feet were elevated for one minute.
2. If blanching did not occur, voluntary forceful flexion of toes and feet was performed for one minute.
3. The feet were lowered to a dependent position to note delay of color return (over one minute) and degree of rubor.
4. The extremities were then observed in the horizontal position.

Of the 100 patients studied, 27 had signs of occlusive vascular disease (table 5). In two cases, amputation of toes had been performed in the service. Fourteen cases showed delay in color return after elevation; 11 had marked delay in venous return (over 20 seconds on the Colens-Wilensky

TABLE IV

Site and Degree of Color Changes with Change of Posture

Posture	Intensity	Cyanosis		Rubor		Pallor	
		Right	Left	Right	Left	Right	Left
Elevation	+					4 ft.	3 ft.
Elevation	++					25 ft.	20 ft.
Elevation	+++					28 ft.	39 ft.
						3 hands	2 hands
Elevation	++++					34 ft.	34 ft.
						1 hand	2 hands
Dependency	+	3 ft.	3 ft.	3 ft.	4 ft.		
Dependency	++	19 ft.	16 ft.	22 ft.	11 ft.		
				1 hand	1 hand		
Dependency	+++	28 ft.	31 ft.	8 ft.	10 ft.		
		3 hands	3 hands				
Dependency	++++	23 ft.	22 ft.	6 ft.	3 ft.		
Horizontal	+	1 ft.	1 ft.				
Horizontal	++	9 ft.	5 ft.				
Horizontal	+++					4 ft.	7 ft.
Horizontal	++++						

Postural color changes were observed in 96 patients. They were of severe degree in 73 patients.

TABLE V
Character of Pulses

	Good		Moderate		Faint		Absent	
	Right	Left	Right	Left	Right	Left	Right	Left
Dorsalis pedis	38	41	44	37	17	16	2	4
Post-tibial	36	34	45	44	16	20	1	1
Popliteal	30	28	25	21	7	5	1	1

Faint or absent pulses were found in 27 of the patients.

test). Ten patients showed cyanosis of toes and margins of foot, and six showed pallor of these parts. Edema was noted in 29 cases and paronychia in four. Thickening of the skin and callus formation were the most frequent trophic changes encountered; atrophy of the skin was found in only nine cases (table 6).

Hyperhidrosis of the feet was found in 91 of the 100 patients (mild in 44, moderate in 18 and severe in 29). Findings of chronic recurrent

TABLE VI
Trophic Changes

Type of Lesion	Patients
Thickening of skin	32
Scaling	6
Blisters	1
Ulcers	6
Callus formation	27
Atrophy	9
Total	81

phlebitis of deep calf veins (swelling, redness and pain on pressure) were found in only two cases.

The recorded changes concerned the lower extremities and were bilateral in the great majority of cases. Preponderance of involvement of one side was not frequent enough to be of any statistical significance. Only two patients had mild involvement of both hands, and one had mild involvement of the right hand.

The group has been under constant observation for more than one year, and close attention has been paid to the behavior under the marked climatic variations in our area. All patients felt decidedly better during the warm weather and reacted promptly to a cold spell with increase of subjective complaints (coldness of extremities, pain on standing or walking, increase in perspiration, numbness), and decrease in work tolerance. On exposure to extreme heat, increase in perspiration and pain on exercise were listed as complaints; however, these complaints never approached the degree of incapacity noted in cold weather. It is not clear whether their tendency to excessive perspiration is part of this regulatory disturbance. The numb-

ness, burning and tingling, i.e., the sensory disturbances, were interpreted as vascular in origin, because all these patients had objective signs of peripheral circulatory insufficiency in the absence of neurologic or orthopedic findings.

Discussion

The immediate reaction to cold is vasoconstriction in the skin, and dissipation of heat is consequently inhibited. This process is of course reversible. Exposure to cold may, however, lead to immediate tissue death if it is severe enough (the lower the temperature, the shorter the period). Furthermore, if the thermal injury is of moderate intensity but maintained for many hours or days, thrombosis of the minute blood vessels, and finally even of fair-sized vessels, takes place. These two latter processes are obviously not reversible. Under peace-time conditions, many of the frostbite cases we have seen occurred in individuals with impaired arterial blood flow, even when the arterial insufficiency was only partial in some cases. The patient with arterial insufficiency is abnormally susceptible to cold injury.[7, 8] In such cases there is comparatively little tendency to canalization of thrombi, and tissue death will frequently make its appearance.[8, 9] If, however, the exposure to low (but not necessarily freezing) temperatures in connection with dampness occurs in otherwise perfectly healthy individuals with no impairment in the peripheral circulation or its regulation, the results could be expected to be somewhat different. The last war provided us with a mass experiment in that field; the cases reported here are representative of this latter group.

The following is our concept of the development of the chronic phase in trench foot. Recanalization of the thrombosed blood vessels or development of collaterals must have occurred to prevent tissue death in most of these men; consequently there arose no need for amputation in the majority of them. Only 27 per cent present findings indicating occlusive vascular changes. Among the remaining 73 per cent about half exhibit even bounding pulses in the arteries of their feet. However, what does remain in all of those we have seen is impairment of regulation of blood flow. These men continue to show postural color changes, a tendency to scaling and the development of blebs, sensitivity to cold, and a symptom comparable to intermittent claudication in cold weather. A good many of them have also acquired sensitivity to heat and a tendency to hyperhidrosis. The mechanism involved in the production of hyperhidrosis is not clear from the present evidence. Sterile inflammatory reactions [10] in the rest of the tissues in the limb, probably including the nerves,[11] may have taken place. Such sterile inflammation in the chronic phase, however, is not perceptible clinically and presents no specific manifestations. In contrast, the vascular disturbance is evident.

From these observations it appears that chronic trench foot is a pe-

ripheral vascular disorder resulting in functional insufficiency, chiefly expressed in failure of regulation of blood flow in response to external stimuli.

Summary

1. Close scrutiny of a group of 100 cases suffering from the chronic phase of trench foot has yielded further support to the concept that this condition is essentially characterized by a disturbance in regulation of peripheral blood flow.

2. The most incapacitating feature of the disease is abnormal sensitivity to cold with a symptomatology comparable to intermittent claudication.

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TUBERCULOUS PERICARDITIS: A REPORT OF THREE CASES TREATED WITH STREPTOMYCIN *

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THE treatment of tuberculosis had been generally supportive until Hinshaw and Feldman [1] in 1945 demonstrated the efficacy of streptomycin in human tuberculosis. Their report followed that of Schatz, Bugie and Waksman,[2] who in 1944 demonstrated the in vitro inhibitory effect of streptomycin on the tubercle bacillus. In tuberculous pericarditis, some employed the introduction of air into the pericardial sac after the withdrawal of fluid in an effort to help decrease adhesion formation. This form of therapy has not been unequivocally accepted as effective.

Reports of the use of streptomycin in tuberculous pericarditis are few in number, and only seven were found in the American and foreign literature. McDermott et al.[3] reported its success in a 22 year old female. Streptomycin was given initially for a three month period for pulmonary involvement following a miliary spread. Ten weeks after the cessation of this initial course of streptomycin the patient developed signs of pericardial and pleuritic involvement. A six week course of streptomycin was then given, and two and one-half months after the end of this course she was asymptomatic. Meredith [4] reported its effective use in a 17 year old Negro who was asymptomatic three months after discharge. Tubercle bacilli were not isolated from the pericardial fluid, but a lymph node biopsy showed tuberculosis and there was a co-existent pulmonary infiltration. Johnson and Bercu [5] reported three cases: the first was a 59 year old white male who one year later was in excellent health; the other two cases were Negro youths who became asymptomatic after its use. Cloetens [6] of Belgium reported a case in a white male with associated renal, rib and vertebral tuberculosis, with apparent recovery from the pericarditis. Jervell [7] of Norway reported the case of a 27 year old white male who, five months after discharge from the hospital, was well and working. A pericardial tap was not done, but a cold abscess over the trochanter proved to be tuberculous and thus strengthened the impression that the pericarditis was of tuberculous etiology. Mouriquand et al.[8] of France reported the use of streptomycin for 27 days in a 19 year old white female who had a proved tuberculous pericarditis. Six weeks after the completion of the streptomycin course she was completely well, with no evidence of previous pericardial involvement. Ebert and Falk,[9] during the Eighth Streptomycin Conference in November, 1949,

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reported 16 cases of tuberculous pericarditis which were made available by the coöperative units studying streptomycin therapy. Six were improved, three unchanged, one was worse and six were dead. All of these cases, however, were a select group having cardiac decompensation. Seven additional cases had a pericardiectomy with streptomycin as an adjunct. In this group, six were improved and one died.

McDermott used 3 gm. daily intramuscularly for six weeks; Meredith, 0.2 gm. intramuscularly every three hours for 33 days; Johnson and Bercu, 0.1 gm. every four hours intramuscularly for 13 days; 0.5 gm. intramuscularly every 12 hours for 120 days, and 0.5 gm. intramuscularly every 12 hours for 42 days, in their three cases, respectively; Cloetens, 50 gm. in 36 days; Jervell, 0.5 gm. every 12 hours for 28 days; and Mouriquand, 26.5 gm. in 27 days. Ebert and Falk reported variable dosage and duration of treatment. The most frequent regimes were 1 to 2 gm. daily for 60 or 120 days.

Because of the relative rarity of reported cases of tuberculous pericarditis treated with streptomycin, the following three cases are reported.

Case Reports

Case 1. A woman, then aged 24, developed pulmonary tuberculosis in 1935. She was first seen at this hospital in 1942, where a diagnosis of bilateral, far-advanced pulmonary tuberculosis was made. She was started on a left extrapleural pneumothorax, which was converted to an oleothorax in 1942. The pericarditis probably started about November, 1946, with signs and symptoms of caval obstruction. There was progressively increasing venous pressure, decreasing blood pressure and hepatic enlargement during her hospital stay. Serial electrocardiograms showed pericardial involvement. The cardiac shadow on roentgen-ray showed gross generalized enlargement. Pericardial aspiration was attempted by a right parasternal approach; the usual approaches were not used because of the large left extrapleural space. Only a few milliliters of straw-colored fluid were obtained by this route. Streptomycin, 0.375 gm., was administered every three hours intramuscularly for a period of three and one-half months, at which time it was stopped because of severe vestibular disturbances. The pulmonary pathology began rather promptly to respond favorably to the streptomycin, cardiovascular improvement with lessening signs of caval obstruction occurring gradually after several weeks. When next seen here eight months later, the patient's pulmonary and pericardial disease was judged to be inactive. There was nothing to suggest previous pericardial involvement. Her sanatorium physician reports that she has maintained an excellent general condition, that the venous pressure is normal, and that the sole evidence of former pericardial involvement is a very slight persistent pericardial friction sound.

Case 2. A 26 year old white woman, seen for the first time in 1941, had the onset of her pulmonary tuberculosis about 1939. In 1941 a diagnosis of bilateral, far-advanced fibrocavernous pulmonary tuberculosis was made. The onset of signs and symptoms of pericarditis was about March, 1948, three months prior to her third hospital admission. There had been progressive exertional dyspnea, orthopnea, edema from the umbilicus to the feet, and right epigastric pain. A sudden attack of dyspnea accompanied by substernal pain occurred shortly after entry. There were cyanosis, venous engorgement and a blood pressure of 80 mm. Hg systolic and 60 mm. diastolic. The liver was palpable 5 cm. below the right costal margin, and

the lung bases were clear. The clinical impression was tuberculous pericarditis and mediastinitis, with resultant caval obstruction. The venous pressure was 240 mm. The electrocardiograms showed marked digitalis effect, which would mask other factors. The initial chest roentgenogram showed probable generalized cardiac enlargement, but accurate determination was not possible. The left border could not be visualized because of overlying pulmonary disease. The right border, however, extended halfway from the spine to the parietes. About one month later cardiac fluoroscopy demonstrated adhesive pericarditis, with a thin plaque of calcification over the right anterior surface and possibly on the left as well. Determination of cardiac size again was not definite. On July 1, 1948, the patient was started on streptomycin, 1 gm. intramuscularly daily, which she received for 30 days. There was continued progressive improvement on streptomycin and digitalis, so that on discharge at the end of August the venous pressure was a normal 78 mm. She was thought to have made a complete clinical recovery from the pericarditis and mediastinitis. Reports from the sanatorium revealed that there were occasional periods of dyspnea following discharge and some progression of the pulmonary disease. She died suddenly in April, 1949, of a massive hemoptysis. An autopsy was not obtainable. The sanatorium physician's final diagnoses were far advanced pulmonary tuberculosis, quiescent, and healed tuberculous pericarditis with associated cardiac and caval obstruction.

Case 3. A 29 year old white male who entered the hospital in April, 1949, had the onset of his pulmonary tuberculosis about December, 1947. His pericarditis probably started about two weeks prior to his hospital entry. For these two weeks tachycardia, malaise and a daily temperature of 99.2° to 102° F., as well as left posterolateral basilar sharp chest pain were present. He was quite toxic. Physical examination suggested a moderate sized pericardial effusion. Cardiac fluoroscopy, after the replacement of a small amount of pericardial fluid by air, revealed a fluid level. The venous pressure was 190, the blood pressure averaged 120 mm. Hg systolic and 80 mm. diastolic. There was no clinical evidence of increased venous pressure other than the elevation detected on direct measurement. Serial electrocardiograms showed progressive changes characteristic of subacute pericarditis. The pericardial fluid was negative for acid-fast bacilli on smear and culture, although the sputum was positive. At the time of the pericardial tap, 0.1 gm. of streptomycin was placed in the pericardial cavity. The patient was given dihydrostreptomycin, 1 gm. intramuscularly daily for 45 days, beginning on May 1, 1949. At his sanatorium he had been given streptomycin for a four month period beginning eight months prior to his hospitalization, so it was gratifying that he responded to the streptomycin therapy with a rapid objective and subjective improvement. He was readmitted one year later, in April, 1950, because of persistently positive sputum. There was no clinical or roentgen-ray evidence of his having had pericardial involvement. He had gained 15 pounds in weight and was in excellent general condition.

Summary

Three cases of tuberculous pericarditis treated with streptomycin are reported. Although the number of streptomycin-treated cases of tuberculous pericarditis is too small for any definite evaluation of this form of treatment, the prompt, persistent improvement of the pericarditis suggests its efficacy. Further study is indicated to confirm these results and to determine the optimal dosage and length of treatment.

The author wishes to thank Dr. H. A. Dickie for her helpful suggestions and for the privilege of studying these cases.

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LIVER FUNCTION TESTS IN NONSPECIFIC ARTHRITIS WITH SPECIAL REFERENCE TO HYPERGLOBULINEMIA *

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FOR years some students of arthritis have tried to connect rheumatoid arthritis with some vague hepatic deficiency, perhaps a hepatic dysfunction in the nature of a failure of the detoxifying function of the liver. But the idea has not been susceptible of proof, since no significant pathologic lesion in the liver has been noted,[1] and since a few studies with different tests of hepatic function have shown no consistent hepatic insufficiency.[2]

While other investigators [3] have used a variety of liver function tests in rheumatoid arthritis, only a few reports [4] are available on results with the cephalin-cholesterol flocculation and the thymol turbidity tests in this disease. What is more, a survey of the literature fails to reveal any reports on the concurrent use of the cephalin flocculation test, the thymol turbidity test and the A/G ratio in a series of arthritis cases. As we frequently use these three tests simultaneously in those of our patients suspected of having liver damage, it was thought advisable to use this group of tests in a series of cases of nonspecific arthritis.

Inasmuch as recent studies [5] on remissions in nonspecific arthritis would tend to indicate that many of the measures employed in the treatment of rheumatoid arthritis are hepatotoxic in nature and may influence the results of liver function tests, all of the tests in this study were carried out prior to instituting any therapy.

CLINICAL DATA

This group of patients consists of 20 cases of chronic nonspecific arthritis. Of these, 10 were typical instances of rheumatoid arthritis, eight had the clinical characteristics of osteoarthritis and two were individuals in whom the proliferative and degenerative changes of both forms of the disease were present in the same patient, the so-called mixed form of nonspecific arthritis.[6]

The clinical data on these cases are presented in table 1. For the most part these patients were ambulatory. They ranged in age from 22 to 68 years. As is usually the case, the average age of the rheumatoid group (42 years) was less than that of those suffering from osteoarthritis (52 years). Of the 20 patients, 16 were female and only four male, a somewhat higher incidence of females than is found in larger series of cases.[7] The disease varied in severity. Three cases were classified as mild, 12 as moderately severe and five as severe. The duration of the arthritis ranged from four

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TABLE I

Clinical Data in 20 Cases of Nonspecific Arthritis

No. of Case	Name	Sex	Age	Type	Duration	Severity
1	G. Y.	F.	42	Rheumatoid	4 months	Moderate
2	H. D.	M.	68	Rheumatoid	2 years	Mild
3	A. S.	F.	49	Rheumatoid	2 years	Moderate
4	H. L.	M.	26	Rheumatoid	2 years	Moderate
5	J. B.	M.	38	Rheumatoid	1½ years	Moderate
6	O. M.	F.	22	Theumatoid	1 year	Moderate
7	E. J.	F.	45	Rheumatoid	5 years	Severe
8	L. C.	F.	67	Rheumatoid	7 months	Moderate
9	T. F.	M.	42	Rheumatoid	4 years	Severe
10	M. K.	F.	26	Rheumatoid	3 years	Moderate
11	R. W.	F.	71	Osteoarthritis	4 years	Severe
12	H. G.	F.	66	Osteoarthritis	2 years	Moderate
13	S. T.	F.	68	Osteoarthritis	4 years	Severe
14	A. M.	F.	46	Osteoarthritis	1 year	Mild
15	A. G.	F.	44	Osteoarthritis	2 years	Moderate
16	M. G.	F.	47	Osteoarthritis	1½ years	Moderate
17	I. P.	F.	47	Osteoarthritis	4 years	Moderate
18	E. G.	F.	66	Osteoarthritis	2 years	Moderate
19	B. R.	F.	71	Mixed	7 months	Severe
20	E. B.	F.	66	Mixed	6 months	Mild

months to five years in the rheumatoid group, and from six months to four years in the patients with osteoarthritis.

METHODS AND NORMAL VALUES

The cephalin flocculation tests were done by the Hanger [8] method. While many workers consider a 2 plus reaction significant, we have found a 2 plus flocculation in normal subjects and do not consider a flocculation of less than 3 plus abnormal.[9]

The thymol turbidity tests were done by the Shank and Hoagland [10] modification of the method introduced by Maclagen.[11] The upper limit of normal accepted by most investigators is four to five units.

The biuret method of Kingsley [12] was used to determine the total serum protein and the albumin in the filtrate, after precipitating the globulin with sodium sulfate according to the method of Howe.[13] With this method the normal value for serum protein is 6 to 8 gm., the albumin range is 4 to 5.5 gm., and the upper limit of the globulin is approximately 3 to 3.2 gm.; a globulin between 3.2 and 4.5 is considered moderately elevated, and values of more than 4.5 are regarded as markedly increased. By the same method, the range of the A/G ratio is usually given as 1.5 to 2.5, while a figure under 1.2 is considered to be definitely abnormal (Loeb, Cantarow and Trumper, Todd and Sanford, Bray, Lichtman [14]).

I am fully aware that with the electrophoretic method, the globulin fraction of the serum protein is somewhat higher and the albumin somewhat lower than with the method of chemical fractionation used in this study.[15] I am also cognizant of the fact that the distribution of the globulin fraction

may be definitely abnormal electrophoretically in spite of a normal A/G ratio on chemical analysis.[14a, 15] Nevertheless, it is interesting to note that in 31 samples of blood examined electrophoretically by six different groups of observers,[16] the A/G ratio of the entire series averaged 1.8, and that the largest single group of 12 samples in this series also averaged 1.8. As the average A/G ratio determined chemically is about 2, it is obvious that for practical clinical purposes the A/G ratio may be determined chemically as well as by electrophoresis.

Results

The cephalin flocculation tests were negative in all of the 20 cases of typical rheumatoid, osteo- and mixed arthritis. The thymol turbidity test was likewise negative in all of the 15 patients on whom the test was done.

As noted in table 2, the serum protein was estimated in eight of the 10 patients with rheumatoid arthritis. All of these had serum protein values within normal range. The same was found to be the case in eight patients with osteoarthritis who had serum protein determinations. Both patients with mixed arthritis had a normal serum protein.

In this group of 18 patients, only three had a serum albumin less than 4 gm. and, of these, only one was truly significant, with a figure of 3.4.

Of the eight rheumatoid cases, seven had a globulin over 3 gm. and, of these, one was over 4.5. Of the eight osteoarthritis cases, seven had a globulin over 3 and one was 4.3. The two mixed cases had globulin figures of 3 and 4.2, respectively. Of the 18 patients who had A/G ratios done, the result was less than 1.5 in 15 instances and below 1.2 in five cases.

Discussion

Our findings with the cephalin flocculation and the thymol turbidity tests are in marked contrast to the results of some other observers who in the past have investigated liver function in chronic arthritis. Rawls, Weiss and Collins [3a] in 1937 found that liver function as measured by the azorubin S test was impaired in 55 per cent of their patients with rheumatoid arthritis. In 1939,[3a] the same authors reported that 60 per cent of a series of 50 unselected cases showed some impairment of liver function with the azorubin S test, 62 per cent with the oral hippuric acid test, 48 per cent with the bilirubin excretion test and 14 per cent with the galactose tolerance test. They also reported an abnormal icterus index in 44 per cent of their cases. More recently, Carter and Maclagen [4a] reported positive cephalin flocculation tests in 13 of 34 patients with rheumatoid arthritis (26 per cent), and noted also a high percentage of positive thymol turbidity tests in a group of 17 cases of rheumatoid arthritis (82.4 per cent). On the other hand, Kunkel,[4b] using the thymol turbidity test, reported a maximum figure of 12 units but an average of four units (normal range) in seven cases of rheumatoid arthritis.

Inasmuch as these investigators of liver function in arthritis apparently have not considered the possibility that many of the agents employed in the treatment of rheumatoid arthritis are hepatotoxic in nature,[5a] it is quite reasonable to believe that the results of their liver function tests may have been influenced by therapy, unless a base was established by checking liver function prior to treatment. As pointed out in another communication,[5] it has been found that when serial cephalin flocculation and thymol turbidity tests are done in cases of nonspecific arthritis during therapy with gold salts and other potentially hepatotoxic agents, the liver function tests, originally negative, may become positive. The fact that in the present study the liver function tests were done prior to therapy may help to explain the difference between our results and those reported by others.

As already noted, other investigators, using both chemical fractionation and the electrophoretic method, have reported on the serum protein and the A/G ratio in chronic arthritis.[3c, 3d] These workers seem to agree that the total blood protein is normal in most of these patients but that there is a tendency toward an elevation of the serum globulin in patients with rheumatoid arthritis. Our findings are consistent with these reports.

It is of interest to note that this tendency toward an elevation of the serum globulin is present in patients with osteoarthritis as well as in cases of rheumatoid arthritis.

It seems important to stress the fact that the tendency toward a lowering of the A/G ratio in nonspecific arthritis is not the result of a diminished albumin and a correspondingly elevated globulin, as seen in parenchymatous disease of the liver,[17] but is the result of an elevated globulin alone. In this connection it should be emphasized that hyperglobulinemia is not, per se, an indication of liver damage, inasmuch as this biochemical change is present in a number of conditions in which there may be no hepatic disease. A list of such conditions includes multiple myeloma, lymphopathia venereum, sarcoidosis, lupus, subacute bacterial endocarditis, and a miscellaneous group of diseases comprising malaria, syphilis and tuberculosis.[18]

Summary and Conclusions

1. Twenty cases of nonspecific arthritis were tested for evidence of liver damage prior to therapy, using the cephalin-cholesterol flocculation test, the thymol turbidity test and the A/G ratio.

2. The cephalin flocculation and the thymol turbidity tests were consistently negative in all of these patients.

3. The total serum protein and the serum albumin were found to be normal in this group of patients, but there was a tendency toward an elevation of the serum globulin.

4. Because of the elevated globulin, there is a tendency toward a lowering of the average A/G ratio in patients with nonspecific arthritis. How-

TABLE II

Results with the Cephalin-Flocculation, Thymol Turbidity and A/G Ratio in 20 Cases of Nonspecific Arthritis

No. of Case	Type	Total Protein (gm. %)	Albumin (gm. %)	Globulin (gm. %)	Albumin-Globulin Ratio	Thymol Turbidity (Units)	Cephalin-Cholesterol Flocculation	
							24 hrs.	48 hrs.
1	Rheumatoid	7.7	4.3	3.4	1.24	3.2	Neg.	Neg.
2	Rheumatoid	—	—	—	—	0.7	Neg.	Neg.
3	Rheumatoid	8.1	4.4	3.7	1.19	4.8	1+	2+
4	Rheumatoid	8.0	4.8	3.2	1.5	0.3	1+	1+
5	Rheumatoid	5.8	3.8	2.0	1.4	0.1	1+	1+
6	Rheumatoid	8.2	3.6	4.6	1.27	1.7	1+	2+
7	Rheumatoid	8.0	4.2	3.8	1.1	3.8	1+	1+
8	Rheumatoid	7.5	4.2	3.3	1.28	0.8	1+	1+
9	Rheumatoid	—	—	—	—	2.4	Neg.	Neg.
10	Rheumatoid	7.6	4.2	3.4	1.24	—	1+	2+
11	Osteo	8	4.5	3.5	1.29	0.7	Neg.	1+
12	Osteo	7.4	4.4	3.0	1.46	0.5	1+	1+
13	Osteo	6.9	3.4	3.5	1.0	1.0	Neg.	Neg.
14	Osteo	8.3	4.0	4.3	0.93	3.1	Neg.	1+
15	Osteo	8.24	5.4	2.8	1.9	1.2	Neg.	Neg.
16	Osteo	7.5	4.5	3.0	1.5	—	Neg.	Neg.
17	Osteo	8.0	4.5	3.5	1.3	—	Neg.	1+
18	Osteo	7.2	4.0	3.2	1.25	—	Neg.	1+
19	Mixed	7.2	4.2	3.0	1.4	2.4	1+	1+
20	Mixed	8.3	4.1	4.2	1.0	—	Neg.	1+

ever, the albumin-globulin pattern which is present is not that associated with parenchymatous disease of the liver.

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RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS (WEBER–CHRISTIAN DISEASE); REVIEW OF LITERATURE AND REPORT OF CASE *

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DEFINITION

RELAPSING, febrile, nodular, nonsuppurative panniculitis is a title that defines a disease, which is characterized by recurrent episodes of fever ranging as high as 104° F., and by the formation of single to multiple crops of tender or painless, freely movable, inflammatory and necrotic nodules in the panniculus adiposus. The nodules do not produce pus and may regress in a few days or weeks, either leaving a shallow dimple in the skin or showing no superficial evidence of their site. The nodules range from about 0.5 to 3 cm. in diameter. The overlying skin may be normal in color but usually is red or violaceous. The temperature over the lesion may be that of the skin elsewhere or warmer.

Relapses occur at intervals as short as a few weeks and as long as several years. There are no prodromal symptoms. The subcutaneous nodules can occur on any part of the body but appear most commonly on the legs, abdomen, breasts and arms.

HISTORY

Pfeiffer [1] first described this disease adequately in 1891 as a croplike atrophy of the subcutaneous fatty tissue. It was not until 1925 that Weber [2] described a similar case which he called relapsing, nonsuppurative, nodular panniculitis. Christian [3] then reported the third case in 1928, adding "febrile" to the final title of the disease. Since then, almost 50 additional cases have been recorded in the literature.

Because of its usually benign nature, and because of the little space devoted to it in textbooks, the disease is undoubtedly much more common than is realized, and frequently goes undiagnosed.

ETIOLOGY

Thus far the etiology of relapsing, febrile, nodular, non-suppurative panniculitis is unknown. The etiologic factors to be considered are as follows:

Halogen Compounds: Bromide and iodide medication was first brought under suspicion by Weber [2, 4]; and Keil,[5] in a general discussion of panniculitis, concluded that these halogens caused this particular form of pan-

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niculitis. Bailey [6] thought that iodine therapy was the possible cause in four of his cases, and noted an exacerbation of crops of nodules after the re-administration of iodine in three. Rosenberg and Cohen [7] described two cases, both having a history of bromide medication prior to onset of disease. After withdrawal of bromides, both patients were free of panniculitis, but one developed lesions again within 48 hours and the other one a month after resuming bromide therapy. Niedermayer and Moran [8] associated a definite remission of symptoms with discontinued use of iodine-containing drugs and iodized salt. Larson and Ootkin [9] showed that application of iodine to the skin of sensitive individuals produced a histologic picture resembling that of relapsing, febrile, nodular, nonsuppurative panniculitis. Likewise, this same response was reproduced by the subcutaneous injection of camphor in oil, insulin and paraffin.

Shaffer [10] tried unsuccessfully to bring about an exacerbation with the administration of potassium bromide and potassium iodide in a case of "liquefying, nodular panniculitis," an entity which fits the clinical course of and is possibly the same disease as relapsing, febrile, nodular, nonsuppurative panniculitis. The nodules in this form of panniculitis become centrally liquefied, break down, and discharge a sterile, yellow, oily fluid. Bunnell and Levy [11] described a similar occurrence at the site of biopsy. However, the majority of case reports give no history of bromide or iodide medication, and the blood levels of these elements were normal.[11, 12, 13, 14]

Infectious Agents: (*a*) *General Discussion.* No organism has been consistently demonstrated in the reported cases of relapsing, febrile, nodular, nonsuppurative panniculitis. Alderson and Way [15] described a single case in which a streptococcic infection appeared to initiate the disease, which recurred for eight years after the infection cleared. The following studies revealed nothing consistent: urine and blood cultures; agglutination tests for *E. typhosa, E. typhosa O & H, S. paratyphi, S. Schottmülleri, Proteus* OX_2, OX_{19}, and *OXK, P. tularensis* and *Brucella* spp.; cultures of involved skin lesions; animal inoculation of extracts from skin lesions; cultures for anaerobic and aerobic bacteria, amebae and tubercle bacilli; skin tests for tuberculosis, coccidioidomycosis and trichinosis; skin tests with staphylococcic and streptococcic toxins; stool examinations and cultures, and blood and spinal fluid serologic tests. Examinations for microfilariae, Weil's and Bang's diseases have been negative. Nasal smears have been negative for the lepra bacillus, and sputum examinations for tubercle bacilli and fungi have been negative. The Frei test has not been reported positive. No organisms have been seen on stained sections, and the microscopic picture is not in keeping with viral disease with balloon degeneration and inclusion bodies.

(*b*) *Virus.* Shaffer [10] prepared a Berkefeld filtrate of the aspirated contents of an early lesion from his case of "liquefying panniculitis" which produced no reaction when injected intracutaneously or subcutaneously.

(*c*) *Focal Infection.* Foci of infection were thought to have exerted some influence in several reported cases. One of Pierini's [16] four patients seemed to recover after the removal of septic tonsils. Bailey [6] noted dental and tonsillar disease in several of his cases. Many of the reports show associated dental infection. On the other hand, Larkin, DeSanctis and Margulis,[17] and Baumgartner and Riva [18] observed that foci of infection may be removed with no apparent alteration in the course of the disease.

Binkley [19] noted the frequent association of diseased teeth and tonsils, rheumatism and obesity with this form of panniculitis. Skiöld [20] agreed that it might be a form of rheumatism, since focal infection seemed to play an important rôle in both diseases.

Miller and Kritzler [21] performed the autopsy on the first case believed to have died of the disease, and reported no demonstrable focus of infection. Mostofi and Engleman's [22] Filipino patient, in whom the panniculitis was the probable cause of death, also showed no foci of infection at autopsy. Likewise, other cases which lived on with relapses showed no demonstrable foci of infection.[17, 23]

(*d*) *Septicemia.* In the case reported by Ives,[24] where the diagnosis was not confirmed by biopsy, the cause was attributed to an organism entering through a lesion in the hand. No specific organism was named and the blood cultures were negative. Arnold [23] suspected some infectious agent of being the cause in his patient, because she seemed to respond to sulfapyridine medication and suffered five immediate relapses on reduction of the dose or discontinuation of the drug over a period of a year.

(*e*) *Tuberculosis.* Carol, Prakken and van Zwijndregt [25] were of the belief that tuberculosis was a factor in their two cases because of its suspected associated presence, and suggested further that relapsing, febrile, nodular, nonsuppurative panniculitis might be an acute or subacute form of Darier-Roussy's sarcoid. However, the latter-named disease does not show such periods of remissions as panniculitis.

In the case of a Chinese male, Tilden, Gotshalk and Avakian [26] found at autopsy typical skin manifestations of relapsing, febrile, nodular, nonsuppurative panniculitis and extensive tuberculosis. However, no relationship could be shown between the co-existent diseases. Two of the four cases of panniculitis in Argentineans reported by Pierini, Irigoyen and Ugazio [16] had tuberculosis, and these authors noted a similarity of relapsing, febrile, nodular, nonsuppurative panniculitis to macronodular, indurative tuberculosis.

(*f*) *Renal Failure.* Spain and Foley [27] described a 51 year old female who apparently died of uremia as a result of chronic glomerular nephritis and at autopsy gave no clue for the cause of the associated panniculitis.

(*g*) *Dietary Deficiency.* A dietary deficiency was stressed by Tilden, Gotshalk and Avakian,[26] and their patient's lesions cleared simultaneously with the institution of a high vitamin and nutritional diet. Nevertheless,

after this apparent remission, the patient died suddenly eight and a half months after the onset of his illness. The cause of his sudden death was in question by the authors. However, at autopsy extensive tuberculosis was found. Other reports attribute little importance to dietary discrepancies, and Mostofi [22] makes the point that no dietary deficiency existed in his reported case. Reed and Anderson [28] found the ascorbic acid level to be normal in the 30 year old female they followed carefully in regard to diet.

(*h*) *Trauma.* Trauma has been suspected of being a precipitating factor in several sensitive individuals. Binkley [19] observed that his patient bruised readily. Baumgartner and Riva [18] found that one affected with this form of panniculitis would, during a relapse, develop the characteristics of local panniculitis with slight trauma.

Fraser [29] recorded the development of the typical nodules within two to three weeks after an area had been traumatized in a woman with relapsing, nodular, febrile, nonsuppurative panniculitis.

(*i*) *Impaired Fat Metabolism.* Koster and Behr [30] made a chemical study of the blood and fatty tissue from the patient presented by Baumgartner.[18] They proposed the theory that there was a lack of tissue lipase which led to a disturbance in fat metabolism. This in turn resulted in the abnormal composition of fat, causing a granuloma formation. In other words, in place of normal fat disposition there is a disrupted substance which produces a granuloma-forming fat.

(*j*) *Foreign Body Reaction.* Sundwall [31] described a case of a 19 year old girl in whom there were localized areas of atrophy of the fat cells in the derma and subcutaneous tissue. In this girl there was unilateral atrophy of the whole fatty layer involving Scarpa's triangle and an area over the anterior surface of the tibia. There were no cuplike depressions in the skin, but rather an equal, diffuse loss of fat. There was no suggestion of a chronic inflammatory process as seen in relapsing, febrile, nodular, nonsuppurative panniculitis. Tissue sections showed no cellular infiltration or macrophagic process. Gilchrist and Ketron [32] described a case of atrophy of the fatty layer of the skin similar to the above but unique in that there were the added features of a chronic inflammatory picture with large macrophages phagocytizing the fat. Their theory on the etiology of this condition might well be considered in this discussion of relapsing, febrile, nodular, nonsuppurative panniculitis. Here the fat is considered to act as a foreign body which ultimately stimulates an inflammatory reaction. The macrophages from the resting tissue cells, from the endothelium of the capillaries and probably from the connective tissue appear to phagocytize this changed fat. They in turn may liberate it in some soluble, inert form which can be excreted by way of the blood and lymphatics. After the fat has disappeared this inflammatory reaction, its function accomplished, is replaced by fibrous tissue which in itself gradually disappears, leaving the skin practically normal with the exception of the absence of the fatty layer.

(*k*) *Endocrine Disturbances.* So far, no endocrine disturbances have been established.[21] Symptoms were aggravated in one case [23] during menstruation. Basal metabolic rates range on either side of normal, as well as normal. Skull roentgenogram shows normal sella turcica.[33] Skeletal roentgenograms repeatedly have been normal.[10, 11, 12, 18, 25, 34, 35]

(*l*) *Blood Chemistry Changes.* There has been no consistent chemical imbalance in the multitude of studies that have been performed on the cases reported. Blood sugar, chloride, proteins, cholesterol, cholesterol esters, nitrogen, creatinine, phosphorus, calcium, total lipids, fatty acids, lipase, phospholipids, phosphatase, uric acid, bromide and iodine were not out of range of normal in a significant number of cases.

Liver function studies were normal in Bailey's [6] case of a woman who apparently died of her disease. Kritzler [36] recorded the liver studies of a woman who died of her disease and they showed liver damage. The Filipino-American male reported by Mostofi and Engleman [22] showed liver enlargement near the time of death, and the only liver function study that was abnormal was a 1 plus cephalin flocculation. The other two cases upon whom autopsies were performed had associated infections which could account for the moderate liver involvement described, namely, extensive tuberculosis [26] and staphylococcic septicopyemia.[37] Spain and Foley [27] reported no remarkable liver changes at autopsy in their case, who died of chronic glomerulonephritis.

(*m*) *Hematologic Changes.* Baumgartner [38] attempted to make a correlation between the bone marrow and fatty tissue, since the fatty tissue per se has the same embryonal stem as blood-building organs. As an example, polycythemia vera is mentioned in which the yellow bone marrow is converted into blood-forming marrow. The peripheral blood picture shows a wide range of variations from normal red cell count [1, 2, 3, 6, 8, 10, 17, 18, 21, 28, 34, 39, 40, et al.] to anemia.[11, 22, 26, 41] No polycythemia was observed. The leukocyte count was found to vary from leukopenia [5, 8, 21, 22, 24, 35, 37, 41, 42] through normal [2, 6, 9, 10, 18, 23, 26, 28, et al.] to leukocytosis [1, 11, 19, 34] during exacerbations of panniculitis. There has been nothing consistently unusual noted in the differential white blood count.[8, 35] All the sternal marrow biopsies have been reported as normal.[17, 22, 35, 37]

There has been an associated splenomegaly in some of the cases reported,[24, 33, 36, 37] while in others the authors have made a note of the spleen's not being palpable,[6, 35] and it apparently was not palpable in the majority of cases.

(*n*) *Associated Neurovascular Dystrophy.* Steinbrocker, Spitzer and Friedman [43] report one case of relapsing, febrile, nodular, nonsuppurative panniculitis which was complicated by neurovascular dystrophy, the so-called shoulder-hand syndrome. A reflex dystrophy developed on the same side and subsequent to a solitary nodule in the deltoid region. The shoulder-hand syndrome developed insidiously over a period of a few weeks and per-

sisted for about five months after the bout of nodular panniculitis had resolved.

Incidence

A case of relapsing, febrile, nodular, nonsuppurative panniculitis has been described for about every age group. Carol and his associates [25] diagnosed this disease in a six month old female, Larkin, DeSanctis and Margulis [17] in a 23 month old male, Cummins and Lever [12] in two 10 year old females, and Sweitzer [14] in a female of 70 years. However, most of the cases have developed in individuals between 20 and 40 years of age.

This disease has been found in about three times as many females as males. More cases of this form of panniculitis have been reported in the Caucasian race than in any other race. Miller and Kritzler [21] and Weber [2] each reported the disease as occurring in a Jewish female, Tilden, Gotshalk and Avakian [26] in a Chinese male and an Hawaiian female, and Mostofi and Engleman [22] in a Filipino-American. So far, none has been reported for the Negro race.

The geographic range of cases reported has extended from the Scandinavian [20] countries and the British Isles [2, 4] through Europe,[1, 18, 25, 38, 41] South America,[12] United States,[3, 6, 7, 8, 9, 11, 12, 14, 17, 19, 21, 24, 27, 28, 29, 31, 34, 35, 39, 40] and west to the Hawaiian Islands.[23, 26]

There is no apparent seasonal relationship for the occurrence of relapsing, febrile, nodular, nonsuppurative panniculitis. This disease occurs most commonly as a single entity, unassociated with another specific disease. There has been no epidemic. Not more than one member of a family has had the disease. There is no evidence of contagion, and those concerned in the management of a case have never contracted the disease.

The occupations of individuals developing this disease have been highly varied and there seems to be no relationship to type of work.

It has been found in well nourished as well as malnourished individuals. It has been found more frequently in individuals tending to be obese.

Pathology

Pfeiffer [1] first described the subcutaneous nodule as a pale, slightly movable elevation which may be held between the fingers. Christian [3] said that the nodules imparted to the palpating finger the sensation of irregular, beaded or button-like masses, not entirely separated from each other, and extending in a linear arrangement. There were no signs of atrophy or hair loss in the overlying skin. As the tender nodule disappeared it left a depression in the skin as though the fatty tissue had gone. Gross examination showed the nodule to consist of fatty tissue which was thicker and denser than normal; Pfeiffer likened the picture to that of a fibrous carcinoma. He noted various stages of fatty atrophy in the same piece of tissue at the

same time, thereby explaining the development of the depression in the skin. Eventually, the fat in the involved area disappeared entirely.

Pfeiffer described the microscopic lesion as confluent crops of minute inflammatory foci, in subcutaneous fatty tissue, appearing concurrently with the generalized manifestations of the disease. Christian's [42] description of

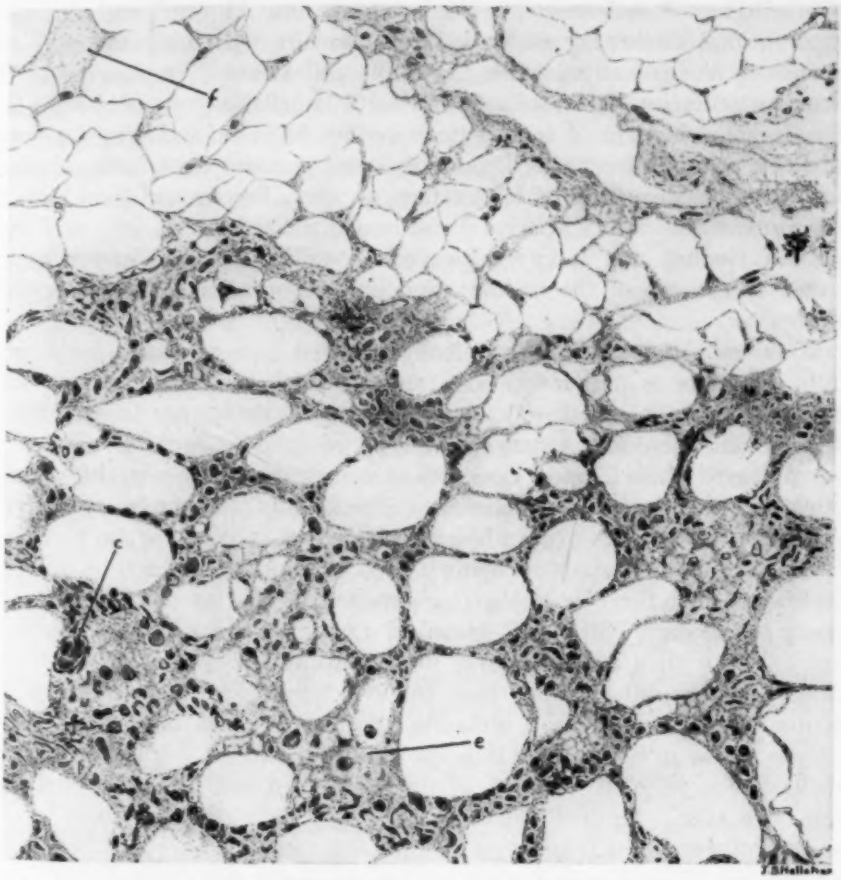

FIG. 1. A composite sketch of the first biopsy taken from case here reported. The upper portion shows uninvolved fat cells and trabeculum. The lower portion illustrates an inflamed fat nodule, the cells of which are crowded by edematous interstices, histiocytes, lymphocytes and plasmacytes.

the histopathologic changes and that of subsequent authors are basically the same. The interstices of the adipose tissue are more or less heavily infiltrated with leukocytes of various types, with separation and partial to complete resorption of fat cells; serous atrophy and even necrosis of fat have been observed. Lipophagocytosis by macrophages is sometimes prominent. The reacting leukocytes comprise lymphocytes, plasmacytes, cells of the

monocyte-macrophage series, and a sparse interspersion of neutrophils and eosinophils. Multinucleated giant cells are occasionally encountered. There is also proliferation of local fibroblasts and reticulum cells. The inflammatory process is singularly limited to the fat lobules proper, intervening fibrous septa and trabeculae being spared (see figure 1).[2, 8, 9, 17, 25, 27, 33, 35] Christian noted that changes in blood vessels were slight and limited to a periarteritis and endarteritis. Niedermayer and Moran [8] and Arnold [23] found intimal thickening of vessels, occasionally with obliteration of the lumen and recanalization, while Cummins and Lever [12] emphasized an increased vascularity of the inflamed fat with lamellation of vessel walls and subendothelial edema. A feature described by Alderson and Way [15] as being consistent was the absence of hemorrhage and pigment deposition. Bunnell and Levy,[11] however, noted hemorrhage in early lesions and focal areas of brown pigmentation. Christian [42] mentioned the absence of fatty acid crystals, but Bunnell and Levy [11] observed crystalline material in small cysts formed at the site of the nodules, and on one occasion a focal deposit of calcium salts.

Eventually, fat cells are completely replaced by scar tissue, which generally contracts to dimple-like skin depressions. In some instances [12] the nodules have disappeared without any trace of their former site. Gilchrist and Ketron [32] described extensive atrophy of subcutaneous fat in an eight year old girl whose clinical course was compatible with relapsing, febrile, nodular, non-suppurative panniculitis. The fat was taken up by large phagocytic cells, the fat cells proper being entirely lost in many areas, producing superficial dimples and actual distortion in contour of the legs. Christian [3] emphasized that there is neither suppuration in the fat nor break in continuity of the skin. Shaffer [10] described a patient having liquefying nodular panniculitis with a clinical course like relapsing, febrile, nodular, nonsuppurative panniculitis, except that the overlying skin became discolored, eventually cyanotic, to form bulla-like membrane which later broke down; a sterile yellow or brown fluid full of fat globules exuded. Individual lesions would discharge 90 to 120 ml. of fluid and then heal, leaving a puckered pigmented scar. Bunnell and Levy [11] thought their case analogous because the patient developed pseudocysts containing sterile fluid. The biopsy site in their case showed poor healing, and broke down and drained during two relapses.

Bailey [6] was the first to describe a patient with relapsing, febrile, nodular, nonsuppurative panniculitis who apparently died of the disease per se, and Kritzler [36] the first to autopsy such a case. Kritzler's patient was a 34 year old Jewish female whose illness lasted 29 months. Shortly before death her temperature rose to 104° F., and chemical studies indicated liver damage. At autopsy, the liver appeared fatty and the spleen was enlarged. There were fat emboli in the lungs, the cells of the adrenal cortex showed hydropic degeneration, and large numbers of erythrocytes were engulfed by cells of the reticuloendothelial system.

Mostofi and Engleman [22] reported the third fatal case, a 38 year old Filipino-American soldier. The microscopic sections from this patient were reviewed at the Army Institute of Pathology, where the diagnosis of relapsing, febrile, nodular, nonsuppurative panniculitis was confirmed. The autopsy disclosed widespread involvement of adipose tissue showing early changes characteristic of this disease. The conspicuous lesions were found in the subcutaneous, epicardial, peripancreatic, periadrenal, perirenal and mesenteric fat. No clue to an etiologic factor was obtained.

Other patients have been autopsied whose death was probably due in part to co-existing diseases. Tilden, Gotshalk and Avakian [26] performed a postmortem examination on a 64 year old Chinese male who had extensive tuberculosis and died eight and one-half months after the initial subcutaneous lesion of panniculitis. Grossly, the previously involved areas appeared essentially normal at time of death, but microscopic sections showed the typical fibrotic replacement of the affected fat; no other remarkable observations were made.

Spain and Foley [27] autopsied a 51 year old Irish male who died of uremia. These authors noted typical nodules not only in the subcutaneous layer, but in the mesenteric, pretracheal and omental fat as well.

Friedman [37] described adrenal cortical changes similar to those noted by Kritzler in a 23 year old female who died of a staphylococcic septicopyemia. Other organs, namely, the heart, lungs, liver, kidney, spleen, brain, bone marrow, endocrine glands, gastrointestinal and genitourinary tracts, showed no evidence of fat involvement.

Clinical Picture

The onset of relapsing, febrile, nodular, nonsuppurative panniculitis is insidious and without prodromata. The patient simply notices the appearance of subcutaneous nodules with or without some overlying reddening. The nodules may be single or multiple. They are usually a few centimeters in diameter, are movable beneath the skin, may be tender and firm, and are most commonly found on the thighs, legs, abdomen, breasts and arms. Nodules as large as 20 cm. in diameter have been described.[28] They have been reported occurring on other parts of the body, including the scalp,[25] neck,[1, 41] hands,[11, 14, 24] and back.[6, 29] Their development may be heralded by chills, nausea, malaise and fever ranging as high as 104° F. Muscle pains and regional adenopathy can occur.[1, 41] The nodules may remain from several days to months, finally regressing and leaving dimples in the skin or disappearing without any superficial trace.[12] Usually, there is no suppuration or break in the skin. The nodules tend to develop during the elevation of temperature.[3]

The spleen [25, 33, 35, 36] may become slightly enlarged.

Fever,[13, 28] as well as the subjective symptoms of nausea, vomiting, malaise and tenderness in the nodules,[22] may be absent either singly or in combination.

Recurrences, with the same clinical findings, occur at intervals of a few days, weeks, months or years. Christian [5, 44] followed his case for six years. During this period the patient experienced 10 relapses, within which time he had a three year interval of complete freedom from symptoms. Baumgartner [38] reported two relapses seven years apart in his case. Individuals have been followed as long as 14 years, with frequent relapses reported.[21] New crops of nodules do not necessarily recur on the same region of the body.

The patient may be so sick during a relapse as to need hospitalization, or be comfortable and capable of carrying on his daily work without interruption. Between relapses, the only evidence or residuum of the disease may be the dimpled skin, representing fibrotic intervals in the fatty tissue which had previously undergone inflammatory changes.

Diagnosis

A diagnosis of relapsing, febrile, nodular, nonsuppurative panniculitis is made on the clinical course, the typical subcutaneous nodules and the histopathologic picture of the nodules. A biopsy is especially important, in cases with an atypical course, in fixing an accurate diagnosis.

The following diseases should be considered in the differentiation of relapsing, febrile, nodular, nonsuppurative panniculitis:

1. *Lipomatosis:* (*a*) *Nodular, circumscribed lipomatosis* consists of single to multiple encapsulated lipomas which are usually asymptomatic and persist indefinitely for many years and do not regress. They are not associated with febrile or other systemic reactions.

(*b*) *Diffuse, symmetric lipomatosis* is characterized by non-encapsulated fatty masses with a predilection for deposition about the shoulders. The masses may be quite extensive, ranging from the neck down the arms, and be arranged in a segmental fashion on the thorax. Systemic reactions are usually absent.

(*c*) *Adiposis dolorosa* (*Dercum's disease*) is characterized by fatty, encapsulated nodules which remain unchanged for years without undergoing atrophy. Alderson and Way [15] described these nodules as being composed of many small, oval, fatty bodies interconnected with each other and with the capsule by delicate fibrous bands. The capsule consists of several layers of well developed connective tissue. There is loose, areolar tissue within the capsule. This tissue is highly vascular, with reticular tissue between the vessels. There may be areas showing granules made up of blood pigment.

2. *Erythema nodosa* may resemble the initial lesions of relapsing, febrile, nodular, nonsuppurative panniculitis, but the nodules do not progress to atrophy of the fat without some change in the overlying skin. The symptom complex may be the same as that in this form of panniculitis with an

antecedent history of the administration of bromides, iodides and sulfonamide drugs.

3. *Erythema induratum* (*Bazin's disease*) likewise is characterized by subcutaneous nodules, but the overlying skin is red or violet in color and eventually turns brown. The nodules usually break down and ulcerate, and tubercle bacilli may in some instances be demonstrated by a smear of the exudate or culture, or guinea-pig inoculation. There is usually no atrophy of the involved fatty tissue.

4. *Sarcoid of Darier-Roussy* is considered the same disease, in its acute or subacute form, as relapsing, nodular, febrile, nonsuppurative panniculitis by Carol, Prakken and van Zwijndregt.[25] However, the nodules do not disappear, as in the panniculitis, and there is no associated atrophy of the fatty tissue beneath uninvolved skin.

5. *Injection sites* for insulin in diabetes and in narcotic addicts may be differentiated by history, inspection of sites and absence of the fatty tissue atrophy in the underlying fatty layer.

6. *Dermatomyositis* is characterized by muscle pain on movement and muscle weakness. The skin lesions are usually not nodular in character, and a microscopic study of the involved skin and muscle will substantiate a diagnosis.

7. *Scleroderma* usually develops more slowly than relapsing, febrile, nodular, nonsuppurative panniculitis, and the diffuse, fibrotic, plaquelike contraction of the skin is the most striking feature. The atrophy of the subcutaneous tissue is more generalized and is not preceded by the nodules of the panniculitis.

8. *Spontaneous panniculitis of Rothman and Makai* is differentiated by Baumgartner and Riva [18] as being a nodular panniculitis with a more symmetrical distribution of lesions. The nodules may vary from about a centimeter in diameter to extensive plaques. There is no reddening of the overlying skin and no associated dimpling.

9. *Gummatous syphilis* generally consists of painless skin lesions and leaves atrophic scars of healing. A diagnosis can be substantiated by a positive serologic test and the results of therapy.

10. *Metastatic neoplasms* and *malignant lymphomas* usually continue to develop when untreated and show no periods of remission.

Prognosis

In only a few cases [6, 21, 22] have the individuals apparently succumbed to their disease, and yet complete recovery is uncertain.

Treatment

No specific therapy for relapsing, febrile, nodular, non-suppurative panniculitis has been reported.

Almost every conceivable therapeutic procedure has been tried, and some authors report a response to their treatment. However, the favorable responses could correspond to the periods of spontaneous remissions. No single apparently successful method has been repeated with the same results by another author.

Supportive and symptomatic treatment thus far is the form of therapy of value to the patient. The application of moist heat locally and bed rest give him the most comfort during the acute stages.

Bacteriostatic drugs have been tried. Sulfadiazine [11, 22, 23, 25, 33] has been ineffectual in most cases in which it has been used; even though Miller and Kritzler [21] noted a remission at the time it was given. Other sulfonamides, such as sulfanilamide,[21] sulfathiazole [11, 23] and sulfamerazine,[11] have been applied without benefit. Arnold [23] administered sulfapyridine to an active case and, on withdrawing the drug on five occasions, noted five relapses within 24 hours, with an elevation of temperature, return of symptoms, increase in sedimentation rate and leukocytosis. On reëstablishing treatment with 3.5 gm. of sulfapyridine per day, conditions returned to normal.

Penicillin has been given in several cases [8, 11, 22] to no avail. However, Zee [33] noted the disappearance of symptoms and nodules after the administration of 20,000 units of penicillin intramuscularly every three hours for 15 days, a total of 2,360,000 units.

The removal of bromide medication in one case [7] and iodine medication in another [8] corresponded to a remission.

Other drugs that have been given a therapeutic trial with this form of panniculitis are quinine,[22] intravenous gentian violet,[6] ferrous citrate [6] and viosterol.[6] Antiluetic therapy has not been found to alter the course of the disease.[1, 6, 10]

Among the heavy metals the salts of antimony,[23] gold,[10, 15] arsenic [15] and mercury [6] have been used without apparent clinical change. Pfeiffer [1] noted a decrease in the size of nodules while giving Fowler's solution, but during its administration new nodules developed.

Roentgen-ray treatment has been tried frequently, to no avail.[6, 15, 28, 37, 39]

Multiple blood transfusions have not influenced the course of this disease in any instance reported.[6, 11, 21] Thyroid and pituitary extracts [15] have not alleviated it.

The removal of foci of infection, especially diseased tonsils, has been stressed by some authors. In one instance [16] the removal was followed by the healing of the lesions, in other cases it had no influence.[17, 18] In addition, the absence of foci of infection has been emphasized.[23, 33, 34]

Case Report

A 39 year old white American male was referred to this office by his local medical doctor on June 10, 1947. He was complaining of feeling generally ill, of recurrent subcutaneous nodules in groin, neck, left cheek and right forehead, and of drenching night sweats, increased fatigability and achy joints.

The patient had had good health until three years before, when he developed a "scratchy" pain in the right lumbar region involving an area about 10 inches in diameter. This pain persisted intermittently for one month, with no apparent cause or local changes, and disappeared spontaneously. At that time a complete gastrointestinal roentgenogram, intravenous pyelogram and complete blood count were made. All findings were within normal limits except that his white blood count was elevated. The impression at that time was that of Hodgkin's disease.

Several months later, in 1944, he developed a firm, painless lump about one and one-half inches in diameter in the left supraclavicular fossa which did not appear to be inflamed. His family physician attempted a biopsy at this time, but the mass seemed to disappear on incision.

A year later, in 1945, he developed an elliptical, painful mass about 3 inches long in the left inguinal region without overlying signs of inflammation. This regressed while being treated locally by a sunlamp and heat. The patient remained the same until about a year before he was first seen at this office (June, 1947), at which time he developed a sharp pain over the left lower chest that made breathing difficult. These pains radiated up to his right shoulder, to his right lower abdominal quadrant and into his left subscapular region. The pains recurred over this period of about a year, lasted a week at a time, and were located in his right shoulder, right hip or left inguinal region. About three weeks before visiting this office, however, his left malar region became painfully swollen and a small lump developed on the right frontal area. The malar swelling became firm and resolved after an ice cap was applied. The lump on the forehead disappeared without treatment. At the time of the present examination there was a painless, fixed, firm nodule in the right temporal region, about 8 mm. in diameter, which seemed fixed to the skull.

For at least five nights in each week for the previous 10 months the patient had been awakened by drenching nightsweats, which became less severe with the onset of warm weather. His temperature had been ranging up to 99.6° F. toward evening. Fatigability had been increasing steadily since onset of ill health. His joints ached at night on retiring and seemed better in the morning on arising. Movement aggravated the pain in the joints.

The patient was given three injections of penicillin, 50,000 units each, two weeks prior to his visit on June 10, 1947, and he believes this reduced his evening temperature.

Systemic Review: The patient had had chronic sinusitis for years, with an acute exacerbation in the left frontal sinus prior to the appearance of the nodule in the right temporal region. He had a postnasal drip, with a cough in the morning productive of about a half-ounce of clear sputum. He had slight vertigo at this time. He had had diplopia all of his life. His teeth had been extracted three years prior to this visit because they were infected. Since that time he had suffered from periodic glossitis. There were no cardiac or other chest symptoms. He had maintained his weight between 180 and 190 pounds in the past 10 years. His appetite was fair and digestion good. His bowel habit was normal and there were no urinary complaints. His complexion had been sallow since onset of present illness.

Family History: His family history was noncontributory. There was no history of a similar disease in the family, and the patient had had no close contact with individuals known to him to have tuberculosis.

Past Medical History: He had had the common children's diseases, and had no history of scarlet fever, diphtheria, rheumatic fever, tuberculosis, pneumonia, typhoid fever or venereal disease. He had had no operations.

Social History: He was a sheet metal worker and came into contact with zinc oxide smoke. He stated he had had the "galvo" shakes on several occasions.

However, none of his colleagues working under similar conditions had complained of nodular swellings. The patient was unmarried and his habits were modest.

Physical Examination: Physical examination revealed a heavy-set, well oriented, coöperative male with a sallow, yellowish complexion who appeared to be his stated age. He was moderately obese, with broad hips, prominent, low abdominal panniculus and with a generally female type of body build and pubic hair distribution. His gait was normal. He showed no signs of weight loss. However, he appeared chronically ill.

On his head in the right temporal region was a 5 mm. nontender hard nodule which seemed fixed to the outer table of the skull and was not movable. There was another firm, slightly tender, noninflamed, slightly movable, 2 cm. subcutaneous mass in the left infraorbital region.

The ears were negative and the left maxillary sinus appeared darkened to transillumination, which was probably due to the overlying mass.

The conjunctivae and sclerae were normal and there was no sign of icterus in daylight. The pupils responded normally to light and accommodation. The extraocular movements were well performed. The media were clear and the discs well defined and of normal color. The venules were moderately engorged but not tortuous. There was a minute, pale area just medial to the left disc.

The patient had complete dentures; his tongue appeared normal and protruded in the midline. The nasopharynx was normal; both tonsils were enlarged and diseased.

The trachea was in the midline; the isthmus of the thyroid was palpable but not enlarged. There were soft, movable lymph nodes at the insertion of the left sternocleidomastoid muscle and in the supraclavicular fossa. There were no other cervical nodes. The axillae were normal and there were several discrete, nontender small nodes palpable in both inguinal regions. There was a questionably palpable left epitrochlear node.

The chest showed a slight scoliosis to the left. The lung fields were entirely clear and no râles were noted. Fluoroscopically the chest was negative. His blood pressure ranged from 120 mm. Hg systolic and 70 mm. diastolic to 140/90. His heart size and configuration were normal. There was normal sinus rhythm and no murmurs were heard.

His abdomen appeared symmetrically obese and there were no scars or striae. No masses, liver, spleen, kidneys or areas of tenderness were palpable. In the areas where deep palpation was performed, small ecchymotic spots appeared. However, no bleeding tendency or petechiae were noted elsewhere.

There were no herniations, and the genitalia were those of a normal, circumcised male. Rectal examination was negative.

There was no clubbing, edema or cyanosis of the fingers or hands. There was definite pallor to the nail beds. Patient had unusually high longitudinal arches. Neurologically, the patient was normal.

Laboratory Studies (June 10, 1947): Urinalysis was entirely negative. Blood count: hemoglobin 11 gm. or 71 per cent; red blood cells, 3,760,000; white blood cells, 7,400, with 69 per cent neutrophils, 28 per cent lymphocytes, 1 per cent monocytes, 2 per cent eosinophils. Blood urea nitrogen: 11 mg. per cent. Fasting blood sugar: 97 mg. per cent. Blood uric acid: 3.7 mg. per cent. Kahn test: negative. Sedimentation rate: 30 mm. in 60 minutes (Westergren method).

The electrocardiographic tracings appeared normal.

Further studies were performed after admission to the Presbyterian Hospital in Philadelphia, as follows:

"Roentgenologic examination of the pelvis and hip, right foot, and right hand show no evidence of bony involvement. There is a small bony exostosis at the distal end of the first right metatarsal on the lateral side." (Edwin L. Lame, M.D.)

Aspiration biopsy of the sternal bone marrow (R. Philip Custer, M.D.) revealed nothing of significance. An aspiration biopsy of the nodule on the left cheek, however, was reported by Doctor Custer as follows: "Sections disclose the fat lobules of the panniculus to be the seat of inflammation of chronic granulomatous type. The fat cells are separated by strands of inflammatory cells, notably lymphocytes and macrophages, many of the latter containing minute fat droplets in their cytoplasm; an occasional multinucleated giant cell is noted. Granular leukocytes are virtually absent from the inflammatory exudate. The several fibrous trabeculae seen in cross sections are quite uninvolved by the inflammatory process. Pathologic diagnosis: Relapsing, febrile, nodular, nonsuppurative panniculitis (Weber-Christian's disease)." (Figures 2 and 3.)

Other laboratory studies performed at the Presbyterian Hospital are as follows: Bence-Jones protein: Negative. Sedimentation rate: 46 mm. in one hour. Red blood cells: 4,030,000 per cu. mm. Serum calcium: 10.6 mg. per 100 c.c. Serum phosphorus: 3.82 mg. per 100 c.c. Serum cholesterol: 301 mg. per 100 c.c. Cholesterol esters: 73 per cent. Total serum protein: 8.14 mg. per 100 c.c. Albumin: 5.51 mg. per 100 c.c. Globulin: 2.63 mg. per 100 c.c. Alkaline phosphatase: 3.4 Bodansky units. Basal metabolic rate: plus 8 per cent. Multiple agglutination tests for *E. typhosa* "O" and "H," *S. paratyphi, S. Schottmülleri, B. abortus* and *Proteus OX–19* were all negative.

The patient remained in the hospital for a period of 11 days, with the gradual disappearance of the nodule on his forehead in about 48 hours. His temperature ranged from 97° to 97.2° F., with the lowest temperatures in the morning and highest in the evening. No medication was administered.

Follow-up Study (February, 1949): The patient remained free of symptoms up until October, 1948, when, after an episode of diarrhea, he again noted subcutaneous nodules and stiffness and soreness in the right shoulder. The right arm became uncomfortably swollen. He developed nightsweats, anorexia, nausea and vomiting. He lost over 10 pounds in the course of about five months.

In addition to the lymphedema of the entire right arm and shoulder, he developed recurrent, nontender, hard small groups of nodules over scalp, forehead and left inguinal region. One firm lump over the left temporal region enlarged to about 4 cm. in diameter. Smaller crops of nodules appeared in a linear arrangement over the right pectoral region.

His temperature ranged from normal in the morning to 99° and 100° F. in the evening.

At no time did the nodules break down and ulcerate or leave depressions in the skin with their regression.

The patient developed cheilosis and glossitis, which cleared temporarily under vitamin B complex therapy. He had a moist cough productive of clear, frothy sputum. Discrete, moderately enlarged right inguinal nodes were revealed, some being 3 cm. in length. His right arm was markedly edematous, with a purplish cyanotic ring encircling the biceps area about 5 cm. in width. There was no tenderness to moderate pressure. He was given roentgen-ray therapy, which resulted in partial impedance of the lymphedema and axillary lymph node enlargement (figures 5 and 6).

The patient was given 4.1 gm. aureomycin hydrochloride for three days and 2 gm. daily for the following four days, with no alteration in his course save reduction in nightsweats. In fact, his arm appeared more swollen during this medication.

A few days later the patient became dyspneic because of a pleural effusion. He was readmitted to the Presbyterian Hospital, and 1,700 c.c. of cloudy amber fluid were removed from the right chest, with relief of dyspnea for two days. It was then necessary to repeat a thoracentesis, and 2,000 c.c. of fluid were removed from the same

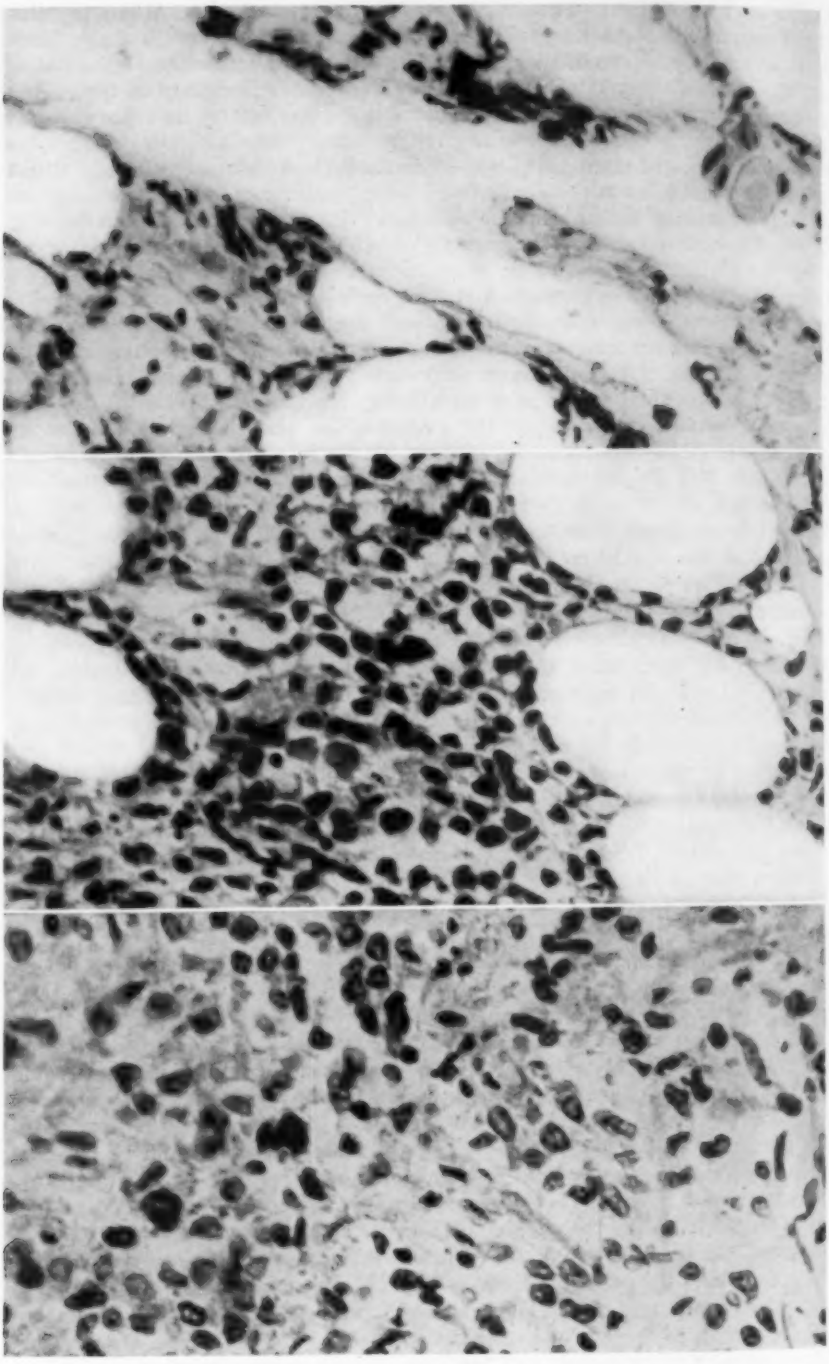

FIG. 2

FIG. 3

FIG. 4

side. The cells in this fluid were concentrated by centrifuging and found to consist of eosinophilic fibrillar material in which lymphocytes, scattered neutrophils and occasional clumps of pleural mesothelial cells were enmeshed. This fluid showed no growth on culture.

Patient was then given 3.5 gm. of sulfapyridine daily for two days without benefit, and this therapy had to be stopped because of toxic symptoms.

He developed painless scrotal edema and penile edema with associated right inguinal adenopathy. The edema lasted several days and cleared without therapy.

The sputum became blood-tinged; concentrated specimens were found negative for tubercle bacilli.

A biopsy of the nodules in the right pectoral region showed adipose tissue heavily invaded by reticulum cells and a paucity of lymphocytes. Because of the recent roentgen-ray therapy and a similarity to the original biopsy in 1947, this was misinterpreted as roentgen-treated relapsing, febrile, nodular, nonsuppurative panniculitis. The site of the 4 cm. incision for the biopsy healed normally.

A spinal needle, with multiple openings filed along its shaft, was inserted its full length under the skin in the forearm, with the drainage of several hundred cubic centimeters of clear edema fluid daily. This gave only slight relief of the severe edema pressure within his right arm.

The patient was given 300,000 units of Crysticillin daily for 30 days, with no dramatic changes in his clinical course; his temperature ranged from 98° to 101.2° F. during this period.

Tincture of iodine applied locally to the skin did not effect visible changes. No foci of infection could be ascertained during this last relapse.

Skull roentgenogram showed normal sella turcica.

The red blood cell count was 4,040,000, hemoglobin 82.5 per cent or 13.4 gm., and the white blood cell count was 7,800, with a normal differential. The serum proteins were 6.5 mg. per cent, with albumin 4.5 per cent and globulin 2.0 mg. per cent. The serum cholesterol was 245 mg. per cent, 41 per cent esters. The blood bromide level was 1.2 mg. per cent; the urinalysis was normal. Immediate injections of material from the lesions into the peritoneal cavities of rats did not show any effect.

The patient's condition grew progressively worse, he became cachectic and died March 18, 1949.

At autopsy* the calvarium showed patchy areas of osteosclerosis and myelofibrosis. The brain showed focal acute meningitis. Each pleural cavity contained approximately 700 c.c. of cloudy thin brown fluid. The diaphragmatic pleura was replaced by a 5 to 10 mm. thickness of sheets of dense, tough, yellow-white tissue which extended partly up the lateral pleural surfaces. Scattered 2 to 3 cm. plaques of similar tissue were seen higher on the parietal pleurae. The nodularity noted under the skin in the right anterior upper chest wall began at the midline and extended to the right axilla. These nodules ranged from 5 to 15 mm. in diameter, were yellow-pink in color and indistinctly defined from the surrounding fat.

FIGS. 2 and 3. *Weber-Christian's disease.* Section through needle biopsy of cheek nodule (1947) showing nonsuppurative panniculitis. Figure 2 illustrates the uninvolved junction between two fat lobules typical of the disease. The cellular exudate separating fat cells is seen in figure 3; there is an admixture of lymphocytes, plasmacytes and histiocytes, with occasional giant cells (not shown). (× 500)

FIG. 4. *Hodgkin's disease.* The complicating tumor responsible for the patient's death (1949) is made up of the usual multiplicity of mesenchymal cell types characteristic of the granulomatous form of Hodgkin's disease. The appearances are superficially those of the original panniculitis, except that the fibroblastic component is richer. In other areas, the tumor had adopted reticulum-cell sarcomatous characters. (× 500)

*Autopsy performed and described by John A. Fust, M.D., Resident Pathologist, Presbyterian Hospital.

The heart weighed 220 gm. The visceral pericardium, particularly above the diaphragm, was so thickened by the infiltration of firm white tissue that it formed a rather rigid shell. The heart also contained various sized nodules in its upper portion.

The right lung weighed 1,200 gm. and the left 1,700 gm. The parenchyma in each was gray and extremely moist. The pleural surfaces were irregularly involved by thick, somewhat inelastic plaques of pinkish-yellow tissue. This was most prominent over the diaphragmatic pleural surfaces, and in this neighborhood the

FIG. 5. Demonstrates marked lymphedema of right arm. Sutures show site of biopsy.

tissue was seen to invade the lung parenchyma. The bronchioles and bronchi of the lower lobes and, to a lesser extent, of the upper lobes were considerably thickened and made rigid by infiltrating white tissue. No focus of bleeding was found. Lymph nodes in the mediastinum were apparently replaced by hard pink-white tissue but did not comprise the bulk of the tumor tissue in this area.

The spleen weighed 220 gm. and had a taut, tough capsule. The parenchyma was bloody, dark red and stippled with 2 to 3 mm. points of soft white tissue which were interpreted as being hyperplastic follicles.

The kidneys weighed approximately 180 gm. apiece. Their cortical surfaces were fairly smooth but there was a fine diffuse pitting. Nodules of tumor tissue were seen haphazardly scattered through the medullae and cortices. The smallest was 5 mm. in diameter and the largest approximately 5 cm. in diameter.

The ureters and urinary bladder were normal.

The stomach was distorted by the mediastinal mass which extended to the superior mesenteric vessels and which was lying on the lesser curvature. There

FIG. 6. Close-up with tangential light showing the nodules of Hodgkin's disease over the right clavicular area.

was a fine seeding of thin plaques of white firm tissue over the serosa of the small and large bowel. A few such plaques were observed on the parietal peritoneum. No evidence of ulceration, hemorrhage or new growth was seen within the bowel.

The liver weighed 2,500 gm. The capsule was smooth and glistening except for fine spots of tumor tissue over its upper surface. The biliary tree was surrounded but apparently not occluded by tissue extending up from the mass lying near the superior mesenteric vessels. The liver parenchyma was grayish-red and the central veins appeared uniformly dispersed and dilated.

The pancreas was encroached upon by the mass of tumor tissue surrounding the superior mesenteric vessels, although fairly well demarcated from it. The pancreatic lobulation had been preserved and the tissue was pinkish-yellow.

The right adrenal was also bordered by tumor tissue lying above it but not involved by it. The cortex was dark yellowish-brown. The left adrenal was completely surrounded by very hard white tissue, although again not invaded.

Microscopic sections of the tumor were typical of Hodgkin's disease with diffuse reticuloendothelial neoplasia, eosinophilic infiltration and Reed-Sternberg cells. Tumor tissue was identified in the lungs, lymph nodes, kidneys, liver, gastrointestinal tract and periadrenal fat.

In none of the sections made post mortem were there any findings suggestive of panniculitis.

The conclusion drawn from this case was as follows: In 1947, at the time of his first successful biopsy, he was ill with relapsing, febrile, nodular, nonsuppurative panniculitis. This was apparently his last relapse, and he later developed and died of Hodgkin's disease.

Summary

A comprehensive study was made of the available literature on relapsing, febrile, nodular, nonsuppurative panniculitis.

1. This disease was first described by Pfeiffer [1] in 1891, and since this time almost 50 additional cases have been reported in the literature.

2. The etiology is unknown. Halogen medication, focal infection, tuberculosis and biochemical disturbances in fat metabolism were discussed as possible factors.

3. The incidence of the disease is variable. It is most commonly found in obese females between the second and fourth decades of life. There is no apparent racial, hereditary, familial, occupational, seasonal or geographic relationship.

4. The involved fat is denser than ordinary fatty tissue. Microscopically, the picture is that of edematous fatty tissue with intercellular, inflammatory, cellular infiltration. At autopsy, similar inflammatory reaction may be noted in other fatty deposits of the body.

5. Clinically, this disease is characterized by the incipient development of single to multiple nonsuppurative, subcutaneous nodules, with fever and malaise. These episodes may last several days to months and may recur at intervals of a few days to years. The inflammatory nodules may regress, leaving a depression in the skin marking their former site.

6. A diagnosis is made on the basis of the clinical picture and a biopsy of the involved fat.

7. The prognosis is guarded. Several cases have been reported in which the patient apparently died of the disease. Most cases live with the threat of recurrence of symptoms.

8. There is no specific treatment for this disease.

9. A case is presented of a 39 year old white American male who was followed for over a year and a half and who finally died of Hodgkin's disease.

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INTERSTITIAL GASTRIC EMPHYSEMA FOLLOWING GASTROSCOPY; ITS RELATION TO THE SYNDROME OF PNEUMOPERITONEUM AND GENERALIZED EMPHYSEMA WITH NO EVIDENT PERFORATION *

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Pneumomediastinum or pneumoperitoneum that appears after gastroscopy is often attributed to a rupture of the esophagus or stomach during instrumentation. Since the introduction of the rubber-tipped flexible gastroscope, however, this complication has been encountered only infrequently. In over 3,000 gastroscopic examinations, representing the combined experience of the authors, such an accident has yet to occur. Only 10 perforations in 22,351 examinations were reported to Schindler [1] by 60 gastroscopists in response to a questionnaire. Of the eight gastric perforations, five were with the sponge-tip and three with the finger-tip gastroscope. The other two cases were a perforation of the hypopharynx and one of the jejunum.

Pneumoperitoneum following gastroscopy without evident visceral perforation is being encountered with increasing frequency. Six case reports have been published. Schiff, Stevens and Goodman [2] were the first to cite an instance in which a considerable amount of unsuspected free air was found under both diaphragms four days after an uneventful gastroscopy. The patient had no symptoms and, were it not for the preliminary fluoroscopy prior to routine roentgen-ray examination of the gastrointestinal tract, he would not have been known to have a pneumoperitoneum. It is possible, therefore, that other such cases are being overlooked.

The other five reported cases were promptly recognized at the time of gastroscopy. Schindler [3] suspected a perforation in his patient because the stomach collapsed immediately after being inflated and only a fleeting glimpse of a grayish-white membrane was obtained. After removal of the gastroscope, the patient complained of distention and faintness. Pneumoperitoneum was present clinically. The air escaped with a whistling sound when laparotomy was performed three hours later, yet no lesion was found even after the stomach had been inflated with oxygen under 60 pounds of pressure. This patient made an uneventful recovery.

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Berk [4] reported a similar experience. After facile introduction of the gastroscope a normal light reflex was obtained, but then the stomach immediately collapsed. The patient complained of a sense of fullness and tightness substernally but no pain. The temperature, pulse, blood pressure and blood count remained normal. Twelve hours later, after the patient developed a chill and abdominal pain during a glucose infusion, the abdomen was explored. On opening the peritoneum, air escaped with a whistling sound. No tear in the stomach or abdominal esophagus could be demonstrated.

Chamberlin [5] passed the instrument easily but noted difficulty in inflating the stomach. A large amount of mucus was present and the ulcer was only momentarily visualized. After the examination the patient belched copiously. The abdomen was distended and emphysema of the scrotum was noted. The leukocyte count was 20,000. Temperature, pulse and respirations were normal. When operation was performed the peritoneum was under marked tension, and a gust of air escaped when it was entered. Emphysematous blebs were noted on the lesser curvature extending into the fundus. Marked retroperitoneal emphysema was observed over the aorta. An ulcer crater on the posterior wall, 2 cm. in diameter, was resected. The mucosa was velvety, edematous and grayish-white. The lymphatic and perineural spaces were noted to be dilated, and the author suggests this as the possible pathway for the air. Three days later emphysema was present in the neck and suprapubically.

Lichstein and Wharton [6] encountered minimal resistance just beyond the cardia after introducing the gastroscope. The mucosa was visualized and, beyond it, a slitlike opening which widened when the stomach was inflated and then drew together. The lips of this slitlike opening were smooth and not indurated. The patient was pale but in no distress. Liver dullness was replaced by tympany. The patient was explored and it was estimated that several hundred cubic centimeters of air escaped from the peritoneum. No lesion was demonstrated even after the stomach was distended with air.

The sixth case, reported by Gilbert, Knight and Dalton,[7] had coöperated well and the scope was passed without difficulty. There was a fleeting glimpse of mucosa before the stomach wall collapsed. It was impossible to inflate the stomach. When surgery was performed three hours later the peritoneum pouched into the incision. Upon opening it a loud gust of air escaped. The stomach was half-filled with water but no perforation could be demonstrated.

As suggested by these authors,[7] a certain pattern of symptoms is noted in the cases of pneumoperitoneum without visceral perforation following gastroscopy. It is important to differentiate this condition from the pneumoperitoneum resulting from an actual tear of the stomach wall after instrumentation, since surgery is indicated in the latter. It will be the purpose of this paper to elaborate the syndrome of pneumoperitoneum with-

TABLE I

Syndrome of Pneumoperitoneum without Obvious Perforation Following Gastroscopy

Review of Literature

	Passage of Instrument	Inflation of Stomach	Collapse of Stomach	Symptoms	Signs	Air Pressure in Pneumoperitoneum	Emphysema	Recovery
Schindler 1945	Easy		Blacked out. Fleeting gray-white membrane	Faint and distended	Normal T.P.R. Signs pneumoperitoneum	Whistling escape of air. Marked increase	No mention	Uneventful
Berk 1945	Easy		Blacked out	Fullness and tightness. No pain	Normal T.P.R. and blood count. Signs pneumoperitoneum	Air escaped. Whistling sound. Marked increase	Not mentioned	Uneventful
Lichstein and Wharton 1948	Catch at cardia		Slit-like stoma deflated slowly	Distention. Pale. No distress	T.P.R. normal	Escape of air. Marked increase	No mention	Uneventful
Chamberlin 1947	Easy	Increased resistance	Great deal of mucus. Ulcer momentarily visualized	Distention. No pain. Copious belching	Normal T.P.R. Temp. 12 hours. Leukocytosis 20,000. Signs pneumoperitoneum	Gust of air escaped. Marked increase	Emphysema of scrotum. Emphysematous blebs. Retroperitoneal emphysema	Uneventful
Gilbert, Knight, Dalton 1949	Easy	Increased resistance	Blacked out	Patient unable to belch. No pain or discomfort. Abdomen distended	T.P.R. normal	Peritoneum pouched into incision. Escape of air audible. Marked increase	Air in omental bursa and blebs in gastrohepatic ligament	Uneventful
Fierst, Robinson, Lasagna	Easy	Increased resistance	Triangular opening. Billowing white membrane covered with branching blood vessels	Pale. Epigastric pressure sensation	T.P.R. normal. Shift to left with slight leukocytosis	Hissing escape of air. Marked increase	Diffuse emphysema of mediastinum, carotid sheath and retroperitoneum 2 hours after gastroscopy	Uneventful

out perforation (see chart), and to present a case which demonstrates a mechanism whereby the air may enter into the peritoneal cavity, mediastinum, retroperitoneal space and subcutaneous tissues.

Case Report

In April, 1944, a 51 year old white male had a hematemesis of 500 c. c. and passed tarry stools. Roentgenologic examination of the gastrointestinal tract failed to disclose the source of hemorrhage. During the next three years the patient was completely free of symptoms despite a nonrestricted diet. In May, 1947, however, the patient vomited an estimated liter of blood. The roentgenologic examination revealed a constant irregularity in the pyloric region, with slight gastric residue and a delay in the emptying time of the stomach. Surgical exploration was advised but refused. The patient was placed on a bland six-meal dietary régime with antacids, and had no symptoms until July, 1948.

Fig. 1. Penetrating ulceration of lesser curvature of the pars media.

He was seen by us in the gastrointestinal clinic of the Maimonides Hospital for the first time on August 20, complaining of epigastric pain. Roentgenologic examination revealed a penetrating ulcer niche on the lesser curvature of the pars media of the stomach (figure 1). He failed to respond to an ambulatory ulcer régime, and on September 10 gastroscopic examination was performed.

The Eder flexible Schindler type gastroscope was used. No difficulty was encountered in passing the instrument through the cardia to the deep position, but when the stomach was being inflated a distinctly increased resistance to the introduction of air was noted. In order to obtain adequate visualization, more than the usual amount of air had to be insufflated into the stomach. The antrum was visualized

as a slitlike triangular opening with prominent honeycombed rugae suggestive of hypertrophic gastritis. The stomach remained inflated but appeared rigid. Peristalsis was absent. As the gastroscope was withdrawn to position TWO, a white velamentous, shining, curtain-like structure, over which several prominent branching blood vessels formed a rete, billowed up before the objective. The appearance was like that seen in the fundus of the eye following separation of the retina. The ulcer could not be visualized because of this white membrane floating before the objective.

Following the withdrawal of the gastroscope the patient complained of some substernal and epigastric pressure. He was pale and had a pulse rate of 90 but was in no acute distress. Pneumoperitoneum could not be demonstrated by physical

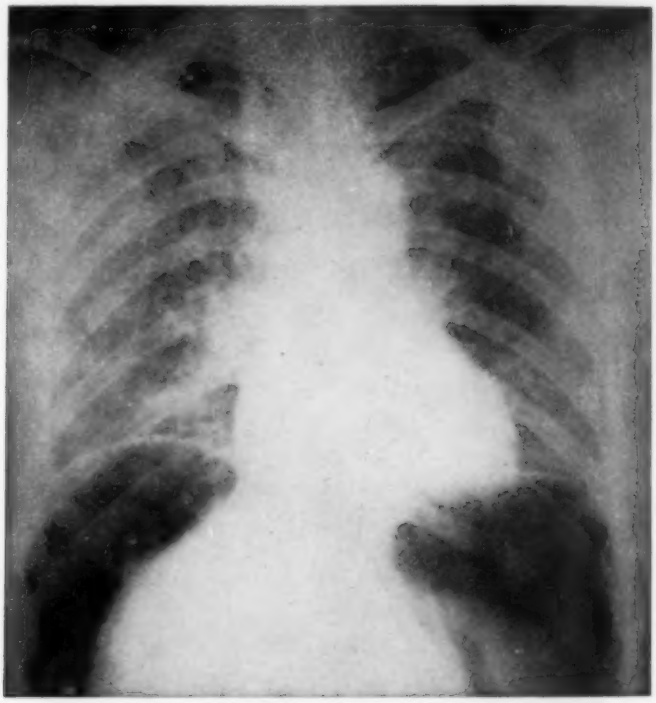

FIG. 2. Pneumoperitoneum demonstrating marked subdiaphragmatic collection of air.

signs. He was admitted to the hospital immediately. Two hours later the patient appeared fairly comfortable but was hoarse and complained of vague pains in the cervical region, shoulders, flanks and abdomen. His neck was moderately swollen, and subcutaneous emphysema was present in the neck, anterior and lateral chest wall, and anterior and lateral abdominal wall down to the inguinal ligaments. The lungs were normal to physical examination. The heart sounds were distant, and to the left of the sternum a "mediastinal crunch" was heard. There was slight tenderness in both lower quadrants of the abdomen, but no masses or organs were felt. The area of liver dullness was diminished. The pulse was 80 per minute, the temperature 98.6° F., the blood pressure 120 mm. Hg systolic and 80 mm. diastolic. The laboratory examination revealed: hemoglobin 12.5 gm., leukocyte count 11,300 with 74 per cent segmented neutrophils, 18 per cent nonsegmented neutrophils, 5 per cent

lymphocytes, 3 per cent monocytes. Urinalysis was normal. Blood sugar was 85 mg. per cent, blood urea nitrogen 10 mg. per cent, serum chlorides 91 mEq./liter, total serum protein 5.63 gm. per cent with 3.2 gm. per cent of albumin and 2.43 gm. per cent of globulin; cephalin flocculation was negative in 48 hours, icterus index 7.2, alkaline phosphatase 4.0 King-Armstrong units, serum cholesterol 172 mg. per cent with 40 mg. per cent of free cholesterol.

Within several hours the area of liver dullness could no longer be outlined. Roentgenograms (figures 2, 3) revealed a pronounced pneumoperitoneum, as well as subcutaneous emphysema of the abdominal and thoracic walls and of the cervical region. Air was present perirenally and in the retroperitoneal structures (figure 4) and mediastinum. One hundred thousand units of penicillin every three hours and

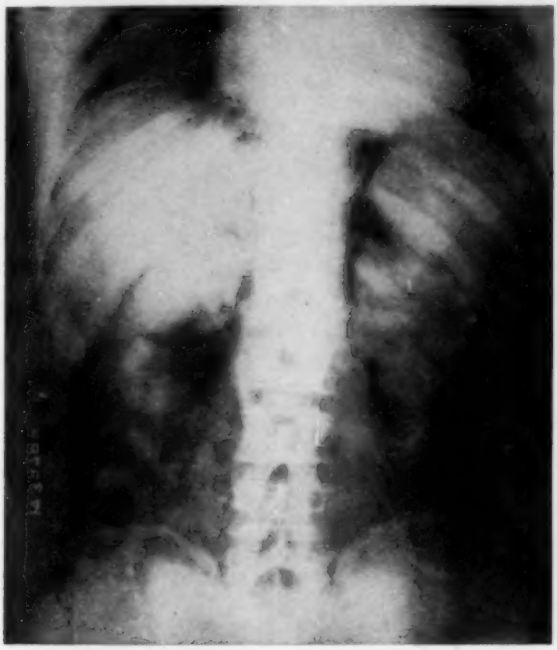

FIG. 3. Retroperitoneal and perirenal emphysema.

0.5 gm. of streptomycin every six hours were administered intramuscularly as a prophylactic measure. Nothing was given by mouth. The blood pressure, pulse, respirations and temperature remained normal. Subsequent white blood counts ranged between 7,500 and 9,100, with normal differential count. Laryngoscopy revealed no involvement of the lumen and no abnormality of the vocal cords. There was no deterioration in the patient's general condition. Nevertheless, since the possibility of a gastric perforation existed, the surgical consultant advised laparotomy, and 24 hours following admission the patient was explored surgically by Dr. A. Mandelberg.

When the peritoneum was opened there was the hissing heavy escape of air under pressure. No free fluid was present in the abdominal cavity. On the lesser curvature of the body of the stomach an indurated, apparently benign gastric ulcer was found. There was no evidence of perforation in this area. The entire stomach

and the abdominal portion of the esophagus were carefully examined, including opening of the lesser sac and examination of the posterior wall of the stomach. There was no evidence of perforation. Extensive vesiculation by air of all the omental structures, especially the gastrohepatic ligament and greater omentum, was noted. Blebs of air were present beneath the serosa of the stomach extending upwards toward the fundus and distally toward the duodenum. There was no evidence of a duodenal ulcer.

The patient made an uneventful recovery. The subcutaneous emphysema gradually decreased and was not demonstrable at the time of discharge on the nineteenth postoperative day. An esophagram performed 13 days after operation was entirely normal.

While at the convalescent home, in spite of adequate medical therapy, the patient continued to have epigastric distress. On November 3, 1948, five weeks

FIG. 4. Carotid sheath and cervical emphysema.

after discharge, he became dizzy and lost consciousness. He was re-admitted to the hospital, where he passed tarry stools and was found to be anemic. He was prepared for surgery with transfusions, and a subtotal gastrectomy was performed. The postoperative course was uneventful and he was discharged symptom-free on November 28, 1948.

The surgical specimen was examined by Dr. A. Kantrowitz. It consisted of a portion of resected stomach and duodenum. An area of firm induration measuring approximately 5 cm. in diameter was present on the lesser curvature. The external surface of the stomach at this area was smooth and glistening, and the remainder of the external surface of the stomach was not remarkable. Upon opening the stomach an ulcer was seen 2 cm. from the pyloric antrum which measured 3.5 cm. by 2.5 cm. and had an excavated and hemorrhagic center. The edges of the ulcer were elevated and appeared firmly indurated for an area about 2 cm. in width on either side of the ulcer. The rugae of the stomach appeared heaped up. The mucosa of the pyloric

portion of the stomach had a cobble-stone appearance. On cut section through the ulcer the excavation was found to extend to a depth of 0.8 cm. It had penetrated through the mucosa and the submucosa, with its apex pointing at the serosa. The base of the excavation had a hemorrhagic appearance.

Microscopically, the entire margin of the ulcerated area revealed the presence of glandular structures varying considerably in size, shape and nuclear appearance. Mitoses were frequent. Shadows of necrotic neoplastic tissue were noted over the ulcerate area. Invasion was noted through all coats to the serosa. The pathologic diagnosis was adenocarcinoma of the stomach.

Comment

The first reaction to finding pneumoperitoneum or emphysema after instrumentation is to attribute it to traumatic rupture of a hollow viscus. It is important to remember that free air in the peritoneal cavity and contiguous tissues may occur without obvious clinical or anatomic evidence of such perforation. Asymptomatic pneumoperitoneum occurring spontaneously has been described in cystic pneumatosis of the intestine.[8] It has been seen as a complication of advanced gastrointestinal scleroderma.[9] Diffuse emphysema extending from the rectum to the base of the skull, infiltrating the retroperitoneal space, subdiaphragmatic region, anterior mediastinum and paravertebral spaces has been described following air insufflation of the colon. Brown and Fine [10] reported such a case during double contrast enema study. Pneumoperitoneum was not present. The patient was asymptomatic and recovered in three days. No tear of the mucosa could be demonstrated by proctoscopy.

In the seven reported cases of pneumoperitoneum without demonstrable perforation of the stomach or esophagus, several explanations have been offered for the presence of the ectopic air. Schindler [3] postulated a tiny tear in the stomach which rapidly seals over, so that even three hours later it is no longer demonstrable. Chamberlin [5] felt that the air seeped through the base of the ulcer or passed through the perilymphatic and perineural spaces. However, the large amount of free air under pressure in the abdominal cavity in all of the reported cases would suggest a different mechanism.

It has been shown by Macklin [11] that when intraalveolar pressure in the lung is increased sufficiently so that the bases of the alveoli bordering on the blood vessels rupture, pulmonary interstitial emphysema results and air enters the perivascular sheaths. The air will dissect its way along these sheaths to the hilum of the lung. The emphysematous blebs formed there rupture, creating mediastinal emphysema and its sequelae. In a similar manner, it can be reasoned that when the stomach is inflated with air during gastroscopy an undue increase in intragastric pressure may occasionally result, either as a result of sphincteric spasm at the pylorus and cardia, or from generalized increased tonus of the gastric musculature. Air might be forced into the perivascular sheaths through a superficial erosion or other weak point in the mucous membrane. The air will travel along the perivascular sheaths until the serosa is reached. Since the serous coat is

very loose, the air can then quickly dissect its way along the peritoneal reflections of the stomach. The air will infiltrate into the gastrohepatic ligament and greater omentum, with large air vesicles forming throughout these structures. When the pressure in them is great enough these vesicles rupture.

Confirmation that air may be driven into the wall of the stomach by inflating it during gastroscopy is found in the work of Myhre and Wilson.[12] They studied 119 patients, 24 hours after gastroscopy, by posteroanterior projection roentgen-ray examination in the erect position. In two cases they were able to demonstrate a line of decreased density surrounding the gastric air bubble. This they interpreted as evidence of interstitial gastric emphysema. There was no pneumoperitoneum and the two patients were symptom-free.

It is also interesting to note that Chamberlin,[5] Gilbert and Knight [7] and this report mention the increased resistance to inflation of the stomach. Brown and Fine,[10] in their colonic case, also noted the increased resistance to inflation, the degree of resistance even suggesting obstruction in the catheter. Pneumatosis cystica of the intestines frequently is associated with spasm or obstruction.[8] Thus evidence exists that some local change in tonus of the muscle may cause an unusual increase in intraluminal pressure which, in rare instances, forces the air into the perivascular sheaths and sets up the previously described chain of events.

In retrospect, the white velamentous structure covered by a prominent vascular rete which we observed billowing into the lumen, the distinct rigidity of the gastric wall and the triangular-shaped antrum with absent peristalsis represented evidence of interstitial emphysema of the stomach with submucosal and subserous penetration of air. Schindler [8] may have caught a glimpse of a similar lifting up of the gastric mucosa, for he described a fleeting white membrane. The white membrane probably represented the mucosa being separated from the vascular submucosa as the air traveled along the perivascular sheaths. When the tissues became permeated with air, peristalsis ceased and the gastric wall became rigid.

The air then proceeded to dissect along the serosa of the stomach into the gastrohepatic and phrenicoesophageal ligaments and into the greater omentum. Emphysematous blebs were formed as seen at operation. Subsequently, several of these presumably ruptured, causing a pneumoperitoneum. The retroperitoneal, mediastinal and subcutaneous emphysema resulted as this process continued. The air passed beneath the serosa along the peritoneal reflections of the duodenum or around the diaphragms to the retroperitoneal space and by way of the phrenicoesophageal ligament and aortic hiatus into the posterior mediastinum and thence into the cervical and subcutaneous region.

It cannot be denied that the air may also extend to the subserous area by direct extension. If there is a chronic ulceration penetrating to the serosa, the air might be forced into the wall along the overhanging edges of

the ulcer and dissect along the subserosa, the subsequent course being identical to that previously described.

All of the reported cases have in common a massive pneumoperitoneum with the air under tension. There is a remarkable dissociation of physical findings and symptoms. It seems unlikely that such a large amount of air could come from a perforation in the commonly accepted surgical sense without more systemic manifestations. In three of the six reported cases, emphysematous blebs were noted beneath the serosa. It follows, therefore, that this symptom complex represents an interstitial gastric emphysema leading to pneumoperitoneum, rather than actual perforation by the gastroscope. The treatment should, therefore, be supportive and conservative. Active surgical intervention should not be necessary. Peritoneal decompression by a needle may be done, in view of the pressure under which the air is found in the peritoneal space.

Summary

1. The symptom complex of pneumoperitoneum and generalized emphysema without demonstrable visceral perforation after gastroscopy is discussed.

2. The gastroscopic appearance of interstitial gastric emphysema is described.

3. A possible mechanism for the spread of air producing the pneumoperitoneum and generalized emphysema following gastroscopy is proposed.

4. It is suggested that, in the absence of systemic manifestations, the presence of a large amount of peritoneal, retroperitoneal and subcutaneous air after gastroscopy does not necessarily indicate surgical intervention. Exploration may be held in abeyance and a supportive régime employed, thus sparing the patient the risk and discomfort of an abdominal operation.

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SARCOIDOSIS. V. THE EFFECTS OF PREGNANCY ON THE COURSE OF THE DISEASE *

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Since Schaumann [1] first called attention to the systemic manifestations of Boeck's sarcoid, the articles published on the various manifestations of this disease have reached voluminous proportions. It is not the purpose of this paper to review the disease or to enter into the controversy which centers over its etiology. Many excellent reviews [2] have been published in recent years, and the reader is referred to these for further information.

It is thought by many workers in the field that sarcoidosis is a non-caseative form of tuberculosis. Certainly it is often difficult or impossible to differentiate the two diseases on the basis of the pulmonary picture alone. It is a well established fact that active tuberculosis is a contraindication to pregnancy. The patients frequently get worse during the pregnancy, when the metabolism is increased, or following the pregnancy, when the temporary splinting of the diaphragm by the abdominal mass is suddenly released. However, we have been unable to find any references to the effects that pregnancy may have on sarcoidosis.

Three patients with active sarcoidosis followed during and after their pregnancies are reported herein.

Case Reports

Case 1. A 31 year old negro housewife was admitted December 29, 1941, to a state tuberculosis sanatorium with a diagnosis of reinfection, pulmonary tuberculosis, minimal B. At the time of admission she had a generalized lymphadenopathy, and roentgenograms revealed bilateral pulmonary infiltration, more extensive on the left. A left primary temporary phrenic was done on January 6, 1942, and repeated on August 4, 1942. The pathologic report on a cervical gland biopsy was: low grade tuberculosis or Boeck's sarcoid. Sputum examinations were negative and tuberculin tests negative to all dilutions to 1:100. An axillary gland was removed December 22, 1942, and the pathology report on this tissue was Boeck's sarcoid. The patient was discharged and her health remained good. Roentgenogram on November 13, 1944 (figure 1) still showed infiltration in both bases. She subsequently became pregnant and, after an uneventful prenatal period, was delivered February 23, 1945.

Roentgenograms of May 15, 1945, showed the chest changes were more pronounced (figure 2), and she was again admitted to the same sanatorium. At this time Kahn, urine, sputum, repeated gastric washings and skin test, 1:100 dilution for coccidioidal infection, were all reported as negative. The patient was again discharged, and films on January 15, 1946 (figure 3) showed a marked improvement

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of the pulmonary changes. The patient remained in good health. Sputum examinations remained negative, and check-up films at three and six month intervals failed to show any appreciable change in either lung. Following another uneventful pregnancy, the patient was delivered of a second child April 3, 1948. No change has been noted on check-up films since the second pregnancy, and the patient has remained in good health. Chest films of both the newborn infants were reported as negative. Roentgenograms of both feet and hands on April 17, 1948, were negative for any bony changes.

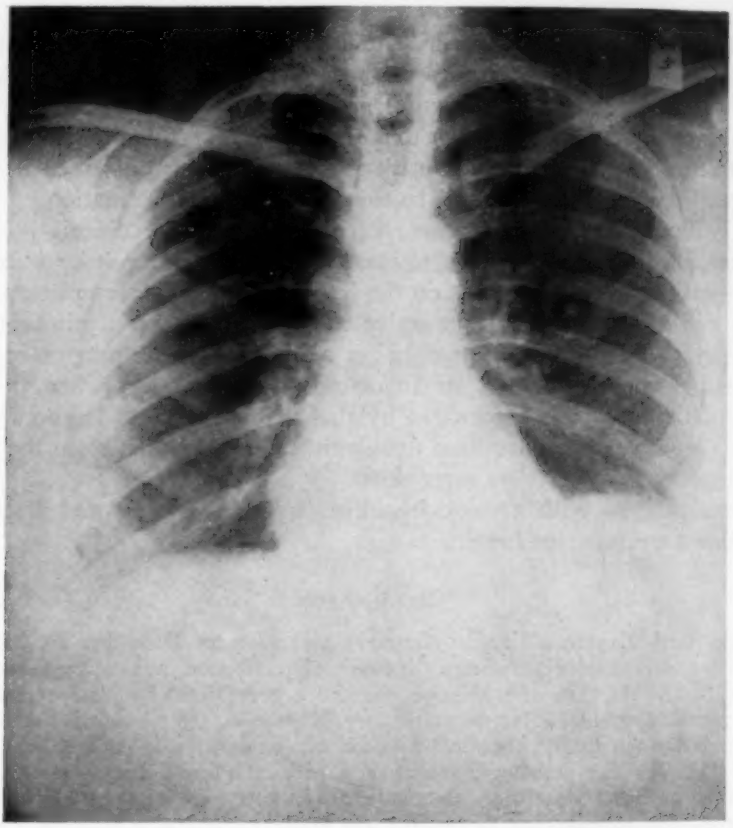

FIG. 1. *Case 1.* Film taken two years after a temporary phrenic on the left, and at about the time pregnancy began.

Case 2. A 28 year old housewife first consulted her physician April 19, 1943, because of a chronic cough. There was no history of fever, weight loss, fatigue or sputum. Roentgenograms of the chest at that time showed a diffuse infiltration in both bases. No definite diagnosis was made and no treatment instituted, as the patient requested that the films be sent to the Tuberculosis Division of the Michigan State Department of Health. A diagnosis of nonspecific pneumonitis was made, with recommendations for further investigation in order to rule out pulmonary tuberculosis. The patient developed a generalized lymphadenopathy and was next seen at the University Hospital. Several glands were removed and the pathology report

stated: widespread infiltration of noncaseating epithelioid tubercles, characteristic of Boeck's sarcoid. The adenopathy was still present in June, 1944, but the patient stated that she was in good health. She was seen again in April, 1945, and at that time she was three months pregnant. In September, 1945, she was delivered of a normal infant. Microscopic examination of the amnion, cord and placenta revealed normal tissue. Periodic chest examinations at various places during the interval between the discovery of the lung disease and the termination of her pregnancy failed to show any appreciable changes in the areas of infiltration. Except for

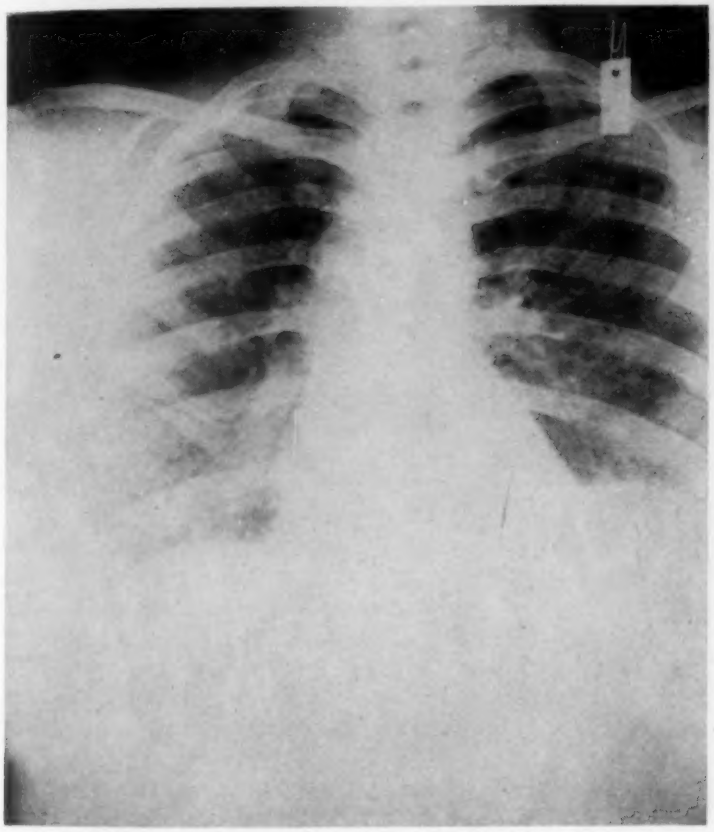

FIG. 2. *Case 1.* Three months after delivery showing the lung changes to be more pronounced than they were before pregnancy.

variations in technic, the films were practically identical. Roentgenograms of both hands and feet were negative except for rarefied areas in the left great toe. The patient then disclosed the fact that she had had a clinical diagnosis of gout, with response to specific therapy for gout, before her first chest examination.

She was next seen in October, 1948, at which time she gave a history of repeated urinary tract infections during the past two years and stated that these attacks were associated with renal colic. At this time her pulmonary changes showed a marked regression. Intravenous pyelograms were normal. In February, 1949, she had a markedly elevated nonprotein-nitrogen and plasma globulin. Sarcoidosis of the kid-

ney was suspected but her condition improved under therapy and she is again apparently in good health.

Case 3. A 34 year old negro woman was admitted to the University of Michigan Hospital in May, 1947, with a two-year history of skin lesions on the face and swelling and pain in several joints. She was six months pregnant. She had had syphilis and several miscarriages during 1941–42. Adequate treatment for syphilis had been given at that time. At the time of admission she had a large fungating granulomatous lesion on the tip of the nose and several pigmented papular and nodular lesions

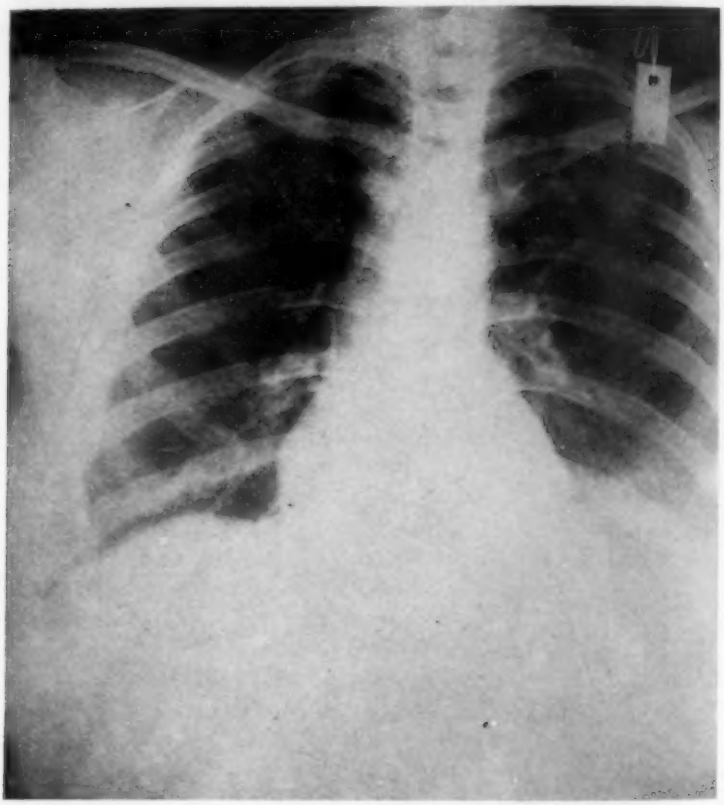

FIG. 3. *Case 1.* Eleven months after delivery, showing improvement but a moderate infiltration.

over the bridge of the nose and onto each cheek. Fingers of the left hand were deformed and right foot and ankle edematous. The Kahn test was doubtful; tuberculin negative 1:10,000 but 1 plus to 1:1,000 dilution. Pathology report of a biopsy from a nodule on the cheek was compatible with syphilis. That of tissue from an amputated left finger revealed noncaseating tubercles, with giant cells in the soft tissue as well as the decalcified bone. Roentgenogram of the chest showed bilateral hilar adenopathy and an increase in lung marking in both bases. Films in search of bone involvement showed destructive changes in phalanges of the left hand and

the distal end of the right tibia and fibula. Cystic areas of destruction were seen in the metatarsals of both feet and phalanges of the toes of one foot. The patient received dihydrotachysterol therapy for her sarcoidosis.[3] She also received intensive penicillin therapy because of the history of lues and the existing pregnancy. No change was noted in lung, skin or bone lesions. In July, 1947, after a normal labor, she was delivered of a normal living child. The dihydrotachysterol therapy was continued until the last week of December, 1947, with continued gradual improvement. The patient was again seen in October, 1948, at which time she was feeling well and the skin lesions had practically healed.

Discussion

Three patients with sarcoidosis were followed during and after pregnancy. All three patient had pulmonary involvement. Two of the patients also had generalized lymph gland involvement, and the third had involvement of the skin and bones.

The pregnancies and postpartum courses were completely uneventful in cases 2 and 3. Normal babies were delivered, and there was no demonstrable change in the course of the disease. Case 2 remained well for three years, when she was again seen for possible kidney involvement, but this certainly cannot be blamed on her pregnancy. Case 3 was followed for one and a half years after delivery and steadily improved during this time.

Case 1 experienced an exacerbation of her pulmonary disease following delivery. This was asymptomatic, but hospitalization was advised for check-up examinations. Her chest cleared considerably within eight months following delivery and has remained the same up to the present time. Her baby was normal, and she has since delivered another normal baby with no ill effects. The exacerbation that did occur in the pulmonary picture was not severe and was of little actual consequence. Although it may well have been related to the pregnancy, the course of sarcoidosis is frequently one of continual change, and this exacerbation may have been purely coincidental.

Conclusions

Three cases of women with sarcoidosis who passed through a normal pregnancy are presented.

No change of significance was observed in the clinical course of the disease during or after pregnancy.

The babies in all instances were normal.

It is believed that sarcoidosis is not a contraindication to pregnancy, and that pregnancy does not significantly alter the course of the disease.

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PURPURA AS A MANIFESTATION OF PENICILLIN SENSITIVITY *

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Introduction

Purpura as a manifestation of penicillin sensitivity has been reported infrequently. Price [1] first reported a "punctate purpuric eruption" occurring in a patient receiving intramuscular penicillin, and noted that the eruption appeared for two days preceding the onset of urticaria, arthralgia, fever, and leukocytosis. Hinman, Warner and Li [2] reported the development of "giant ecchymoses" over the entire body, but most pronounced over the injection sites on the buttocks, in an 85 year old white male, seven days after a scarlatiniform and urticarial penicillin eruption had subsided. Anderson [3] described "an anaphylactic (intestinal) purpura associated with transient swelling of the joints and subcutaneous tissues and a toxic nephritis" appearing in a 37 year old male, following a second course of intramuscular penicillin therapy. Derzavis and Beinstein [4] reported a skin eruption consisting of hemorrhagic vesicles, preceded by an erythematous maculopapular eruption, and progressing to gangrenous ulceration, in a 56 year old white male receiving intramuscular penicillin in oil and beeswax. In a recent review of the literature on penicillin reactions by Brown [5] "based on 308 papers published on this topic between March, 1943, and October, 1948, and an additional 52 papers in which sensitivity is mentioned but neither defined nor described," there are no other reports mentioned on purpura or skin lesions resembling purpura as a result of sensitivity to this antibiotic.

The infrequency of this manifestation of penicillin sensitivity prompted this report of three patients who have recently come to our attention. Hematologic studies were done in an effort to determine the possible mechanism of the production of this hemorrhagic disorder.

Case Reports

Case 1. A 56 year old white male coal miner was admitted to the hospital on December 16, 1948. For the two weeks prior to admission he had received daily penicillin dust inhalations as prescribed by his family physician for an acute bronchitis. Five days after this therapy was begun he noted edema of the lips and eyelids. When first seen in the hospital, he presented a delayed serum sickness type of clinical picture consisting of fever (100.2° F.), arthralgia, generalized joint pain, urticaria, angio-

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edema of the eyelids, lips and dorsum of the hands, and soft tissue swellings about the joints. Four days later he developed purpura on the lower legs, dorsum of the hands and wrists (figure 1), arms and back. Blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. The liver was felt one to two fingerbreadths below the costal margin. The remainder of the physical examination was within normal limits. There was no past history of allergy, previous penicillin administration, or drug sensitivity.

Laboratory Data: Red blood cells, 4,500,000; hemoglobin, 13 gm.; white blood cells 7,600 (polymorphonuclears 64, lymphocytes 32 and monocytes 4). Kahn negative. Sedimentation rate, 23 mm. per hour. Blood platelets, 250,000. Bleeding time (Duke's method) was 1.25 minutes. Coagulation time (capillary tube method)

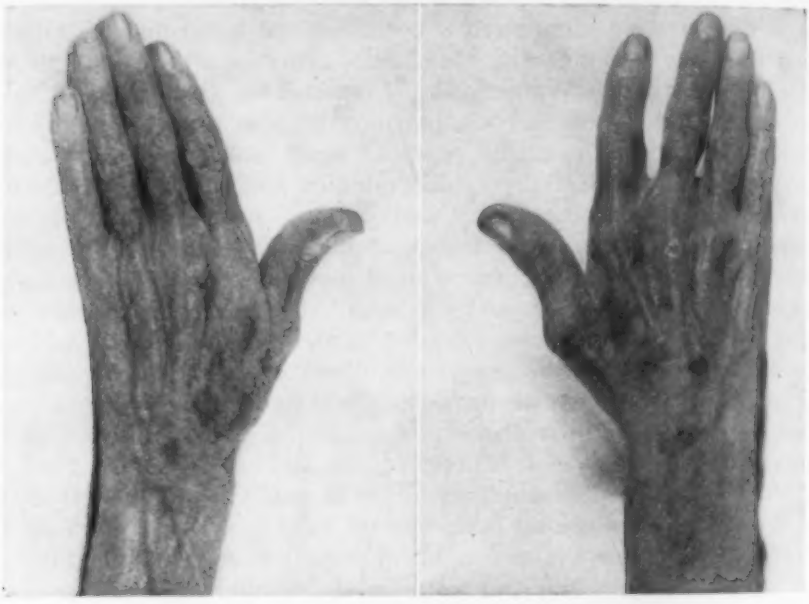

FIG. 1. Case 1, showing purpura of the dorsum of the hands and wrists, due to penicillin sensitivity.

was 3.75 minutes. Prothrombin time (Quick's method) 14 seconds, control 14 seconds. Clot retraction was complete in 24 hours. Urinalysis negative. Serum proteins 7.7 gm. per cent, albumin 5 and globulin 2.7. Liver function studies were normal. Chest roentgenogram revealed evidence of pneumonoconiosis. Electrocardiogram was normal. The tourniquet test (Rumpel-Leede capillary fragility test) was positive. Penicillin intradermal skin test (2,000 units), according to the method of Peck, Siegal, Glick and Kurtin,[6] gave a positive 48 hour delayed reaction. The patient was given antihistaminics and intravenous calcium gluconate. During the next 11 days the purpura faded, the fever subsided, and the urticaria, angioedema and arthralgia disappeared. The Rumpel-Leede test became negative on the sixth hospital day.

Case 2. A 51 year old white male postal clerk was admitted to the hospital on March 1, 1949. Fourteen days prior to hospitalization, his family physician had given him one intramuscular injection of crystalline penicillin and one of procaine

penicillin for symptoms of chronic bronchitis. Nine days later he received a second intramuscular injection of procaine penicillin. The following day he noted redness of the palms of both hands, followed by generalized urticaria, swelling of the eyelids and joint pains. The past history was negative for allergy, previous penicillin therapy and drug sensitivity. Upon admission, he presented the clinical picture of a delayed serum sickness pattern, consisting of fever (103° F.), arthralgia, angioedema of the eyelids, soft tissue swellings of the dorsum of both hands, generalized giant urticarial wheals of the trunk and extremities, and purpura on the fingers, dorsum of the hands, both forearms, ankles and dorsum of the feet. Blood pressure was 110 mm. Hg systolic and 65 mm. diastolic. Remainder of the clinical examination was within normal limits.

Laboratory Data: Kahn negative. Urinalysis negative. Chest roentgenogram negative. Red blood cells 4,680,000; hemoglobin 14 gm.; white blood cells 10,800 (polymorphonuclears 70, lymphocytes 25, monocytes 2 and eosinophils 3). Sedimentation rate, 22 mm. per hour. Blood platelets 282,000. Bleeding time (Duke's method) was one minute. Coagulation time (capillary tube method) was four minutes. Prothrombin time (Quick's method) was 14 seconds, control 14 seconds. Clot retraction was complete in 24 hours. Blood calcium, 11 mg. per cent. Liver function tests were normal. Tourniquet test (Rumpel-Leede capillary fragility test) was markedly positive, with showers of petechiae produced below the blood pressure cuff (78 petechiae per circle 2.5 cm. in diameter). Penicillin intradermal skin test (2,000 units) gave a positive 48 hour delayed reaction. The patient was placed on antihistaminics and intravenous calcium gluconate. During the next nine days the purpura faded, the fever subsided, and the urticaria, angioedema and arthralgia disappeared. The Rumpel-Leede test became negative by the ninth hospital day.

Case 3. A 52 year old unemployed white male was admitted to the hospital for an acute epididymitis on March 8, 1949. He was placed on intramuscular crystalline penicillin, 50,000 units every three hours, for 11 days. Two days after the penicillin was discontinued he developed a delayed serum sickness type of clinical picture, consisting of arthralgia, pruritus, soft tissue swellings of the dorsum of the hands and feet, generalized urticaria, and angioedema of the eyelids. On the eighth day of this sensitivity reaction he developed purpura of the hands, forearms and left lower leg. Bullae filled with hemorrhagic fluid appeared on the fingers and interdigital spaces of the hands. Blood pressure was 122 mm. Hg systolic and 70 mm. diastolic. On auscultation of the chest, there were scattered bilateral musical râles and wheezes. The patient gave a past history of bronchial asthma of four years' duration for which he had been under allergic management. The past history was negative for other allergic diseases, previous penicillin therapy, fungus infections and drug sensitivities.

Laboratory Data: Kahn negative. Red blood cells 4,300,000; hemoglobin 12.5 gm.; white blood cells 10,600 (polymorphonuclears 70, lymphocytes 24, monocytes 3 and eosinophils 3). Sedimentation rate was 20 mm. per hour. Blood platelets 224,000. Bleeding time (Duke's method) was one minute. Coagulation time (capillary tube method) was five minutes. Prothrombin time (Quick's method) 15 seconds, control 15 seconds. Clot retraction was complete in 24 hours. Blood calcium 8.6 mg. per cent. Liver function tests were normal. Chest roentgenogram was negative. Tourniquet test (Rumpel-Leede capillary fragility test) was markedly positive, with showers of petechiae produced below the blood pressure cuff (44 to 54 per circle 2.5 cm. in diameter). Penicillin intradermal skin test (2,000 units) gave a positive 48 hour delayed reaction. The patient was placed on antihistaminics, and during the period of two weeks following the onset of the penicillin reaction, the arthralgias, angioedema and urticaria gradually subsided. The Rumpel-Leede test became negative and the purpura faded on the eighth day following its onset.

Discussion

Allergy to drugs and foods has long been recognized as an etiologic factor in both the thrombopenic and nonthrombopenic types of purpura.[7] Purpura has also been reported as a manifestation of cold hypersensitivity,[8, 9] allergy to inhalants,[10] and in association with serum sickness.[11] It is not unusual, therefore, that purpura should occur as a complication of penicillin therapy, an antibiotic in widespread use and with a high degree of sensitivity reactions.

The action of penicillin on the clotting mechanism of the blood is not completely understood. Divergent views are expressed in the literature in this connection. The studies of Macht [12] show that penicillin produces a marked acceleration in the clotting time of the blood of rabbits and cats. Maldosky, Hasselbrock and Catino [13] report that penicillin decreases the coagulation and bleeding time, whereas Flemming and Fish [14] have reported that the coagulation time of human blood in vitro is increased and the contraction of the clot retarded by penicillin. Lewis,[15] however, has been unable to demonstrate any in vivo or in vitro effects of penicillin on coagulation time, clot retraction, prothrombin concentration, fibrinogen concentration, platelet counts or bleeding time in normal or hemophilic subjects. In their series of patients receiving penicillin, Lewitus and Acchireli [16] found a definite decrease of prothrombin activity in the blood, to a level between 50 to 60 per cent.

The purpura seen in association with the delayed serum sickness pattern of penicillin sensitivity in the three patients reported above is that of a nonthrombocytopenic type. These patients had received no other medication which could possibly account for the onset of this sensitivity. Only one of the patients (case 3) was an atopic individual. There is no doubt that the purpura described in the instances reported above is a part of the allergic picture. Furthermore, in all three instances, other causes of nonthrombocytopenic purpura were ruled out, including infectious diseases, chronic nephritis, cardiac or hepatic disease, food allergy, other drug sensitivities, vitamin C or P deficiencies or hereditary familial purpura simplex. In no instance was it necessary to administer therapeutic rutin or vitamin C, K or P, since the purpura as a manifestation of penicillin sensitivity subsided with the other symptoms upon the cessation of penicillin therapy. In none of the three patients did there appear to be platelet deficiency or disturbances of the clotting mechanism of the blood as determined by normal platelet counts, bleeding time, coagulation time, prothrombin time and clot retraction. The positive Rumpel-Leede tourniquet test that returned to normal when the purpura subsided indicates that the etiologic factor was vascular rather than hematopoietic in origin.

We have observed the tourniquet test to be uniformly negative in patients with urticaria and angioedema as a result of serum sickness and penicillin sensitivity. The positive tourniquet test in these cases of purpura due to

drug allergy probably indicates that the capillaries are in such a state of response that not only is transudation of serum permitted, but also there occurs the actual passage of blood cells through the capillary walls. The negative laboratory findings with reference to the clotting mechanism of the blood, in association with the positive tourniquet tests, probably reflects a more violent and advanced degree of capillary permeability produced as a result of this allergic mechanism.

SUMMARY

1. Three cases are presented of nonthrombocytopenic purpura as a manifestation of penicillin sensitivity.

2. The reported action of penicillin on the clotting mechanism of the blood is discussed.

3. Hematologic studies in all three cases revealed no platelet deficiency or abnormality of the bleeding time, coagulation time, prothrombin time or clot retraction, and the Rumpel-Leede tourniquet test was positive in all three instances, thus indicating that the etiology of this allergic purpura was vascular rather than hematopoietic in origin.

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ARTHRITIS DUE TO INTESTINAL AMEBIASIS*

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THE increased incidence of amebiasis in this country since the war has served to focus attention upon the extra-intestinal manifestations of this disease. These may be classified in two categories:

1. Symptoms due to hematogenous spread of the ameba.
2. Toxic symptoms arising from the primary intestinal focus.

In general the incidence of involvement of extra-intestinal organs is not directly related to the severity of the intestinal lesion. In fact, extra-intestinal symptoms frequently arise in the absence of intestinal symptoms. Furthermore, lesions in organs involved by the hematogenous route may flare up even following the cure of the primary intestinal focus. Thus, extra-intestinal symptoms may so dominate the clinical picture of non-dysenteric amebiasis as to obscure its intestinal origin.

Although any organ may be involved, hepatitis and subsequent pulmonary complications are the commonest sequelae of the hematogenous spread of the ameba beyond the confines of the colon. These complications have been the subject of recent reports [1, 2, 3] and will not be dealt with here.

Many extra-intestinal symptoms have been attributed to amebiasis, which must be considered toxic in nature and secondary to the intestinal infection. These include headache, arthralgia, backache, neuralgia, anorexia, weight loss and fatigue. Klatskin [1] stressed the association of urticaria with amebic infection of the colon. Thus these symptoms, either singly or in combination, produce a variable and obscure clinical picture which commonly suggests a functional origin and simulates psychoneurosis.

Although arthralgia has been listed among the aforementioned symptoms, chronic arthritis due to amebic infection [4, 5] has been rarely mentioned in the voluminous literature relating to amebiasis and arthritis, respectively. It is the purpose of this communication to emphasize the occasional occurrence of this complication, which is clinically indistinguishable from chronic rheumatoid arthritis but, unlike the latter, responds rapidly to specific therapy. In the four cases herein presented the predominant complaint of chronic polyarthritis was associated with relatively mild gastrointestinal symptoms, which were ignored until proved to be of amebic origin. Following the institution of amebacidal therapy, a rapid cure of both the intestinal and arthritic complaints was effected.

* Received for publication April 12, 1949.

Case Reports

Case 1. A 24 year old sergeant with a negative past history developed abdominal cramps and diarrhea while training in Florida in June, 1944, and was treated with sulfaguanidine in a dispensary. The diarrhea subsided after six days of medication, but he noted mild residual abdominal discomfort, for which he sought no further medical advice. He embarked for Australia in July, 1944, and while en route developed rectal bleeding following each bowel movement, which was diagnosed as "hemorrhoids" on the basis of a rectal digital examination. In August, 1944, he experienced painful swelling of the wrists and fingers and was hospitalized for three weeks and discharged with a diagnosis of "rheumatoid arthritis." He returned to duty improved, but reëntered the hospital on October 14, 1944, because of recurrence of swelling of the wrists, phalanges, ankles and knees. During this entire period his bowel movements were regular and formed, and although he noted a small amount of blood in the stool he did not report this finding, due to the previous diagnosis of hemorrhoids. He was treated with salicylates and physiotherapy, with little progress. He then developed pain in both temporomandibular joints which made chewing difficult. He was finally evacuated to the United States and admitted to Schick General Hospital on January 7, 1945, with a diagnosis of "chronic rheumatoid arthritis."

Physical examination revealed a chronically ill young adult male, running a low-grade fever (100.2° R.), with evidence of considerable weight loss. There was swelling of the phalanges, wrists and both ankles. He complained of severe pain on motion of the right shoulder and of the temporomandibular joints. Abdominal palpation as well as rectal digital examination were reported as negative.

Laboratory Data: Hemoglobin 72 per cent; red blood cells 3,910,000; white blood cells 8,900, with polymorphonuclears 80 per cent (segmented 73, stab 7) and lymphocytes 20 per cent; sedimentation rate 24 mm./1 hr. (Westergren). Roentgenograms of the major joints revealed no bone lesions but suggestive narrowing of the interphalangeal spaces.

Continuous bed rest and typhoid vaccine produced little clinical improvement. On February 8, 1945, he reported an exacerbation of rectal bleeding which was accompanied by abdominal cramps and mushy stools. Thus for the first time since the onset of his arthritis was attention directed to the gastrointestinal tract, and he was referred to the Gastrointestinal Section for investigation. Proctosigmoidoscopy revealed several ulcers, averaging .5 cm. in diameter, with hemorrhagic haloes scattered throughout the upper rectum and lower sigmoid. The mucosa between ulcerations was moderately friable and edematous. The ulcers appeared typically amebic, with secondary infection superimposed. Direct smears yielded motile trophozoites of *E. histolytica*, as well as numerous pus cells. Repeated cultures of stools and rectal swabs were negative for pathogens. A barium enema was negative.

Because of the apparent secondary infection, treatment was initiated with a 10-day course of sulfathiazole and sulfasuxidine (1 gm. and 2 gm., respectively, every 4 hours), which resulted in a diminution of abdominal cramps and stool frequency, although visible blood persisted in the feces. This regime was followed by a seven-day course of emetine (1 gr. daily) and the simultaneous administration of carbarsone (gr. 3.75, three times a day), and then by diodoquin (0.63 gm. three times a day) for 21 days. Rectal bleeding ceased on the fifth day of emetine therapy and the stool became formed. Although no direct relationship between the arthritis and the amebic ulcerations was suspected at the outset of therapy, the joint swellings, which had not responded to the sulfonamides, began to recede rapidly after the sixth day of antiamebic treatment. Two weeks after the start of the latter, the patient's sole complaints were muscular soreness at the site of injections and residual stiffness of the jaws. After completion of chemotherapy he was sent home for 30 days and returned

asymptomatic. Proctoscopic examination, sedimentation rate and stools examined for parasites were normal. A communication received from him 14 months later indicated that he had remained free of joint and gastrointestinal symptoms.

Case 2. A 34 year old unmarried female with a negative past history developed acute migratory polyarthritis in September, 1945. This involved her fingers, wrists, right knee and both ankles. Six weeks prior to the onset of symptoms she had returned from a trip to Mexico, where she had enjoyed good health except for a brief episode of diarrhea which subsided spontaneously in 24 hours. She received salicylates, physiotherapy and "injections," with but temporary benefit, as during the subsequent months she noted frequent exacerbations of joint pains, particularly in damp weather. In February, 1946, she developed generalized urticaria of undetermined origin. There was neither a personal nor a family history of allergy. She was placed on an elimination diet but the urticaria continued to recur. Benadryl was tried but discontinued because of disagreeable side-effects. In May, 1946, she noted mild abdominal cramps with a sensation of epigastric fullness and belching. Her bowels were as a rule regular, but occasionally she would have several mushy stools during a 24 hour period. These symptoms were disregarded until she observed a small amount of blood in her stool on one occasion. She was proctoscoped shortly thereafter, with negative findings; a barium enema taken the same day was reported as showing a "spastic colon." A low residue diet with antispasmodics and phenobarbital was prescribed. Although the cramps abated, she continued to complain of bloating, anorexia and weight loss, with exacerbation of arthritis and urticaria. On August 10, 1946, she was referred for investigation.

Essential Physical Findings: Temperature 100° rectal; pulse 82; respirations 14. The patient was a moderately well nourished white female, slightly pale and appearing chronically ill. Urticarial lesions were present over the forehead, neck and forearms. There was mild swelling of the interphalangeal joints; both ankles were tender but not swollen. Although no other joint swellings were apparent, she complained of pain in both shoulders and in the cervical region on motion. The abdomen was soft and presented poorly localized tenderness in its lower half. There were no palpable masses. The liver was neither enlarged nor tender.

Laboratory Data: Urine normal; hemoglobin 67 per cent; red blood count 3,610,000; white blood count 9,200; differential: polymorphonuclears 74 per cent (stabs 6, segmented 65, eosinophils 3), lymphocytes 21 per cent, monocytes 5 per cent; sedimentation rate 28 mm./1 hr. (Cutler); stools were persistently positive for occult blood on a meat-free diet. Proctosigmoidoscopic examination revealed no source of the bleeding. Barium enema disclosed a spastic colon with an incompletely filled cecum, the deformity suggesting spasm of its medial half rather than neoplastic infiltration. The terminal ileum was filled and a loop just proximal to the ileocecal portion showed serration of its margins indicative of active ulceration (figure 1). Serial studies of the small intestine revealed segmentation of the upper half of the ileum and ulceration of the terminal ileum, with a filling defect of the medial half of the cecum (figure 2). Stools were examined following the oral administration of Epsom salts, and numerous cysts and motile forms of *E. histolytica* were recovered. Three stool cultures were negative for pathogens.

Clinical Course: Treatment consisted of emetine hydrochloride by intramuscular route (1 gr. daily for seven days), followed by a 20 day course of diodoquin (0.63 gm. three times a day). Within seven days after the start of this régime there was a remarkable clinical improvement. All abdominal discomfort disappeared and the patient's appetite increased. Urticaria completely subsided and did not recur. Diminution of joint pain was noted on the sixth day, and by the twelfth day the patient was ambulatory. At that time she reported that for the first time since the onset of her illness she was able to move all her joints freely. She was discharged from the

FIG. 1

FIG. 2

FIG. 3

FIG. 1. Double contrast enema (August 11, 1946), showing spastic transverse colon and incomplete filling of the medial half of the cecum. The arrow points to the loop of ileum, with serrated edges due to ulceration. Note the narrowing between this and the terminal portion of the ileum.

FIG. 2. Film taken three hours after the ingestion of barium demonstrating segmentation of the upper ileum, probably due to poor nutritional status. There is loss of normal mucosal markings of the terminal ileum, with serration of the margin of the loop of ileum indicated by the arrow. The medial half of the cecum is unfilled. Barium in the descending colon is the residue from the barium enema given the previous day.

FIG. 3. Three hour film (October 6, 1946) taken four weeks after completion of amebacidal therapy. The previously demonstrated segmentation has disappeared and the terminal ileum is normal. The cecum is almost completely filled and appears normal.

hospital asymptomatic on the sixteenth day. Four weeks later she was reëxamined, at which time she stated she felt fine and had gained 18 pounds. On October 3, 1946, the blood count and sedimentation rate were normal and the stools were negative for ameba. Barium enema and small intestinal series revealed that the segmentation of the ileum, the ulcerations of the terminal ileum and the deformity of the cecum had reverted to normal (figure 3). The patient has remained well during a follow-up period of two years.

Comment: This case presents several unusual features. The most prominent symptoms of amebiasis were arthritis and urticaria, with relatively minor gastrointestinal disturbance despite the radiographic evidence of ileocecal ulceration. While the cecum is the site of predilection for amebic involvement, ileal lesions occur in 5 per cent of cases and their roentgenographic demonstration is rare. Although a nonspecific regional ileitis could not be ruled out in this patient, the concomitant involvement of the cecum suggested the possibility of amebic infection.

Case 3. A 36 year old housewife with a negative past history developed painful swelling of the fingers, right knee and both ankles in May, 1945. A migrating polyarthritis recurred intermittently during the subsequent year coinciding with exposure to cold and following upper respiratory infections. A diagnosis of rheumatoid arthritis was made and she was treated with salicylates and physiotherapy with but temporary benefit. Following an acute exacerbation of arthritis in January, 1946, she was treated with gold injections for three months, with little relief. In May, 1946, she noted progressive fatigue, headache, anorexia and epigastric bloating and belching following meals. Her bowel habits were regular and there was no history of diarrhea. Since symptomatic dietary treatment combined with sedatives gave little relief, she was referred for investigation.

Physical examination was essentially negative, apart from swelling of the right wrist and interphalangeal joints. The left shoulder was tender but presented no visible swelling. There was slight epigastric tenderness with no palpable masses.

Laboratory Data: Urine and blood count normal; sedimentation rate 22 mm./1 hr. (Cutler); stools negative for occult blood; roentgenograms of the hands, wrists and left shoulder negative; gastric analysis normal; gastrointestinal series, gall bladder and barium colon enema normal; gastroscopy normal.

Although her gastrointestinal symptoms were considered to be on a functional basis, stool examination following Epsom salts revealed numerous cysts of *E. histolytica*. Further questioning elicited the fact that she had never been out of New York City and could not recall ever having had diarrhea. Her husband, however, had travelled in the Middle East and had experienced intermittent diarrhea for several years but had never sought medical advice. Subsequent examination of his stools proved positive for *E. histolytica*.

Treatment consisted of a three week course of diodoquin (0.63 gm. three times a day) without the use of emetine. Within two weeks there was a marked improvement of appetite, with complete relief of postprandial epigastric distress. Concurrently her joint pain and swelling disappeared, with but slight residual stiffness of the fingers. Stool examination six weeks after completion of therapy was negative for ameba. The patient has remained asymptomatic for over two years.

Case 4. A 31 year old engineer was stationed in China during the war and while overseas developed mild infectious hepatitis and occasional bouts of "dysentery." He received no medication for the latter and lost considerable weight, but after his return to this country in June, 1945, he regained his lost weight and had no recurrence of diarrhea. In May, 1947, he developed painful swelling of the right wrist,

fingers and left shoulder. A diagnosis of rheumatoid arthritis was made and he was treated with salicylates and "injections," with temporary benefit. He had further flare-ups in July and October, 1947, which again responded to salicylates. In January, 1948, he developed a recurrence of polyarthritis associated with a low-grade fever for two weeks. At that time he noted vague discomfort in the right lower quadrant unrelated to effort, meals or defecation. The pain was described as dull and "nagging," and was present constantly. His appetite remained excellent and his bowels regular. Because of the persistence of this pain he was referred for investigation on March 18, 1948.

Physical examination revealed a well-nourished male, not appearing ill. There was slight swelling of the phalanges, and he complained of pain on motion of the right knee and shoulder and stiffness of the fingers, particularly in the morning. Abdominal examination was negative to palpation. The liver was not enlarged and no tenderness was elicited on punch percussion.

Laboratory Data: Blood count, urinalysis, sedimentation rate, proctosigmoidoscopy, plain film of the abdomen and barium colon enema were normal. Although there was no clinical suggestion of amebiasis, stools were examined for ameba because of his past history of dysentery. Numerous cysts and a few trophozoites of *E. histolytica* were recovered.

Although it could not be determined whether his symptoms were due to amebiasis, the usual therapeutic test was applied. He was treated with a short course of emetine (1 gr. daily for five days), followed by diodoquin for three weeks. Within seven days after the onset of therapy the abdominal pain had completely disappeared. Joint pains subsided after 10 days and did not recur. Stools were negative for ameba eight months after cessation of therapy. At that time the patient reported that he had remained asymptomatic.

Comment: This case demonstrates the protean nature of chronic amebiasis of the nondysenteric type. Although right-sided pain of a constant and "nagging" variety should arouse the suspicion of hepatic amebiasis, the localization of pain in this case was most likely due to cecal involvement, despite negative radiologic findings. In our experience with intestinal amebiasis, positive roentgenographic changes are present in less than 25 per cent of even the dysenteric forms. The presence of trophozoites in the stool is an indication for emetine therapy, in addition to the iodides, even in nondysenteric cases, since the precystic forms of the ameba are not affected by the latter group of drugs.

Discussion

Functional, organic and even anatomic disorders of the intestine have been frequently cited as causes for chronic arthritis.[6] Bassler[7] believes that there is a significant relation between arthritis and a chronic biotoxic intestinal state. While many of the aforementioned etiologic factors are nonspecific and lack confirmation, the relationship between the well-defined chronic colitides and arthritis is an established clinical entity.

Arthritis is a not uncommon complication of idiopathic ulcerative colitis, particularly in cases of long standing, with multiple joint involvement more common than monarticular arthritis. The diagnosis is usually rendered obvious by the protracted diarrhea, although occasionally joint pain and swelling may precede overt intestinal symptoms.

Arthritis is the commonest extra-intestinal complication of bacillary dysentery. Although usually monarticular involving the knee, and commonly accompanied by serous effusion, polyarthritis simulating rheumatoid arthritis may occur. Furthermore, it is more likely to occur weeks or months after the acute phase of the disease has subsided than in the early dysenteric period. Thus Bonnin and Kay [8] recently reported five cases occurring six weeks to eight months after the subsidence of mild bacillary dysentery. Local therapy to the involved joint was of no avail until the intestinal pathogen was eradicated.

Amebic arthritis presents no clinical features distinguishing it from other forms of infectious or rheumatoid arthritis. While only one joint may be involved,[4] as a rule it takes the form of a polyarthritis.[5] Furthermore, the latter is prone to spontaneous remissions, with exacerbations resulting from the same factors that cause flare-ups of rheumatoid arthritis. The main obstacle in the diagnosis of cases hitherto reported,[4, 5] as well as of those in this series, was the relatively insignificant gastrointestinal symptoms. The diagnosis rests not alone upon the isolation of the parasite in the stool, but also upon the favorable response to amebacidal therapy.

The concept has been frequently advanced that many of the clinical phenomena resulting from amebic infection are due to secondary invasion of the ulcers by bacterial pathogens.[5, 9] It might thus be suggested that the arthritis herein reported is due to a similar agent. If the latter were true, then arthritis would be more common in chronic amebic dysentery with extensive ulceration, where secondary infection is an almost invariable accompaniment. Actually, arthritic complications are most frequent in non-dysenteric amebiasis. As was indicated above in case 1, the use of sulfonamides to combat secondary bacterial infection successfully controlled the diarrhea, but no amelioration of joint symptoms occurred until emetine was introduced into the therapeutic régime. In the other three cases, amebicidal drugs were employed exclusively. Although purely speculative, our suggestion is that amebic arthritis is the result of sensitization to *E. histolytica* or its by-products. The combination of urticaria and arthritis in case 2 is highly suggestive of such response to absorption of an intestinal toxin.

The incidence of amebic arthritis is unknown but is probably not sufficiently high to warrant routine stool analysis in all cases of arthritis of undetermined etiology. However, a careful inquiry into past and present gastrointestinal disorders of such patients would undoubtedly prove helpful in determining when such a study is indicated.

Summary and Conclusions

1. Four cases of recurrent polyarthritis secondary to chronic intestinal amebiasis are reported.

2. Amebic arthritis is clinically indistinguishable from rheumatoid arthritis and is subject to spontaneous remissions and exacerbations.

3. In all cases, gastrointestinal symptoms were minimal and arthritic complaints predominated. One patient never had diarrhea, while in another arthritis occurred two years after the last attack of diarrhea.

4. The diagnosis of amebic arthritis was established by the isolation of the ameba from the stools and by the subsequent rapid response of the arthritis to amebacidal therapy.

5. It is suggested that arthritis in these cases was due to sensitization to a toxin elaborated by the ameba, rather than to secondary infection of intestinal ulcers.

6. While amebic arthritis is probably rare, examination of the stools for *E. histolytica* is indicated in all cases of "rheumatoid" arthritis with concomitant gastrointestinal disturbances.

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THE TREATMENT OF PNEUMONIA WITH BACITRACIN *

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In 1945, Johnson, Anker and Meleney [1] reported the discovery of an antibiotic which they called bacitracin, produced by the Tracey I strain of *B. subtilis*. It had a bactericidal spectrum roughly comparable to that of penicillin,[2] and was well tolerated by laboratory animals [3, 4] when applied locally or injected systemically. In 1947, Meleney and Johnson [2] reported the first 100 cases of surgical infections treated locally with bacitracin, with results at least comparable to those obtainable with penicillin. Since then the local use of bacitracin has been successful in the treatment of infections of the skin [5] and eye, and bacitracin has been used intramuscularly in the treatment of a variety of surgical infections and has succeeded many times where other forms of therapy have failed.[6]

At Bellevue we have carried on investigations of the use of bacitracin in the treatment of medical infections. The advantages in having a second antibiotic for use in cases that are resistant or allergic to penicillin are obvious. In addition, the studies referred to [2] indicate that bacitracin can control several strains of bacteria that are not sensitive to penicillin. Therefore, we began the treatment of lobar pneumonia with bacitracin in the spring of 1947. We chose this disease because it was common enough to provide adequate material for study, because we knew that pneumococci were highly sensitive to bacitracin, and because pneumonia is a disease that runs a sufficiently consistent clinical course to facilitate the evaluation of a new method of therapy. We found that doses of bacitracin of 15,000 units every six hours would cure early cases of pneumonia without bacteremia, but were inadequate to clear the blood stream of infection. The supplies of bacitracin available at that time were insufficient to permit the use of higher doses, so further investigation had to be postponed until 1948. The number of cases treated in 1947 was eight, of which five recovered and three had to be changed to penicillin to effect cure.

Material Studied

In March, 1948, the study was resumed and 14 cases of lobar pneumonia were treated with intramuscular injections of bacitracin. Table 1 presents the pertinent clinical data concerning them. There were two females and

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TABLE I

The Diagnosis, Complications, Duration and Results in Patients Treated with Bacitracin

No.	Age	Sex	Diagnosis	Duration Prior to Rx	Days Rx	Complications	Result
1	52	F	Lobar pneumonia RML, RLL	5 days	10	Chr. alcohol.; D.T.'s	Recovered
2	55	M	Lobar pneumonia LUL	4 days	4½	None	Recovered
3	44	M	Lobar pneumonia RLL, RML	5 days	4½	Pl. effusion	Recovered
4	24	F	Lobar pneumonia RML	2 days	4½	Pregnancy; uncinariasis	Recovered
5	53	M	Lobar pneumonia RLL	2 days	5	None	Recovered
6	49	M	Lobar pneumonia LLL	4 days	12 plus 8 aerosol	Empyema; chr. alcohol.; D.T.'s	Recovered
7	48	M	Lobar pneumonia LUL, LLL	2 days	4	Uncinariasis	Recovered
8	48	M	Lobar pneumonia LUL	2 days	4½	None	
9	47	M	Lobar pneumonia RLL	1 day	3	Chr. alcohol.; D.T.'s	Recovered
10	55	M	Bronchopneumonia RLL	3 days	2½	Chr. alcohol.; D.T.'s	Recovered
11	53	M	Bronchopneumonia RML	4 days	8	Bronchiectasis; chr. alcohol.	Recovered
12	37	M	Bronchopneumonia RML	2 days	4½	Serol. lues	Recovered
13	28	M	Lobar pneumonia RML	2 days	2½	Thrombophlebitis; toxic psychosis	Failure
14	41	M	Lobar pneumonia RUL, RML, RLL	3 weeks	22	Acute bact. endocarditis; chr. alcohol.; D.T.'s	Died

12 males in the series, an accurate reflection of the preponderance of males over females admitted to our wards with pneumonia. All but two patients were in the middle age group. All patients had roentgen-ray evidence of pneumonia; most of them had frank lobar consolidations. The illness was of short duration, with one exception (case 14). Many of the patients were alcoholics and contracted their illness as a sequel to exposure during intoxication.

BACTERIOLOGIC STUDIES

The bacteriologic studies on the patients are shown in table 2. In nine cases, pneumococci alone were the infecting organisms; in two cases,

TABLE II

Bacteriologic Data on Patients Treated with Bacitracin

No.	Organism Obtained on Culture of Sputum	Nose	Blood	Bacitracin Sensitivity
1	Pneumococcus Type XIV	XIV	XIV	0.02 units/c.c.
2	Pneumococcus Type I	I	I	0.02
3	Pneumococcus Type II	II	II	0.0062
4	Pneumococcus Type —	—	I	0.015
5	Pneumococcus Type XVII	XVII	XVII	0.04
6	Pneumococcus Type II	II	II	0.0075
7	Pneumococcus Type XIII	XIII	—	0.01
8	Hemolytic Streptococcus	Hemol. Strep.	—	0.015
9	None	None	—	
10	Pneumococcus Type XIV	XIV	—	0.004
11	Pneumococcus Type No Type Hemol. Str.	No Type Hemol. Str.	—	
12	Pneumococcus Type No Type	—	—	
13	Pneumococcus Type XII Hemol. Str.	XII Hemol. Str.	—	0.13
14	Pneumococcus Type II	II	II	0.02

pneumococci together with hemolytic streptococci; in one case, hemolytic streptococcus alone, and in one case no organism could be isolated. This latter was in all clinical respects a typical case of lobar pneumonia of the right lower lobe, and it responded promptly to treatment. Seven patients had positive blood cultures prior to therapy. All the organisms tested were highly sensitive to bacitracin, with one exception (case 13). This case well be discussed later. In case 14, where the blood culture remained positive throughout three weeks of intermittent bacitracin therapy, the organism, a Type II pneumococcus, showed no alteration in sensitivity to bacitracin.

Method of Treatment

Bacitracin was supplied in vials containing from 30,000 to 50,000 units dissolved in 2 to 3 c.c. of 2 per cent procaine hydrochloride solution. The initial dosage schedule was usually 50,000 to 75,000 units intramuscularly every six hours. If a definite response was shown, the dose was usually decreased to 30,000 to 50,000 units every six hours. The duration of treatment and total dosage required varied from 250,000 units in two and one-half days to 3,378,200 units over a period of 12 days. In one instance (case 6), bacitracin was given by aerosol, 10,000 units thrice daily.

The patients were treated for dehydration with parenteral fluids as indicated, and were encouraged to force fluids by mouth as soon as they were able to coöperate. One gram of sodium bicarbonate was given by mouth every four hours to alkalinize the urine. All urine was collected and analyzed for each 24 hour period. Non-protein-nitrogen levels of the blood were taken at the start and at the end of treatment, and in between, every few days, if therapy was prolonged. On some of the patients, phenol-sulfonphthalein excretion and concentration tests were done at the end of the treatment.

In each patient, frequent determinations of the bacitracin level of the blood were made. It has been shown [7] that the highest blood level is observed about one hour after the intramuscular injection of bacitracin, and that the levels fall off gradually after that over a five-hour period. Our levels were usually taken in the fourth hour after the 6 a. m. injection, and for that reason represent minimum rather than maximum levels. They are shown in table 3. Eagle [8] demonstrated that the renal excretion rate of bacitracin is similar to the glomerular filtration rate. We observed that in our patients the higher levels were found in the first 24 to 36 hours of treatment, a period in which oliguria due to dehydration was present. Later, when renal output had increased, lower blood levels were obtained.

Results of Treatment

In this series of 14 cases there were 12 recoveries, one death, and one failure of response. In the recovered patients the fever dropped by crisis in

seven cases, and by lysis in five instances (figure 1). The patient who failed to respond to bacitracin (case 13) was subsequently controlled with penicillin therapy.

It may be of value to comment briefly on the fatal case (case 14). This patient developed an acute endocarditis due to Pneumococcus II, following resolution of an extensive pneumonia under bacitracin therapy (figure 2). After bacitracin in doses of 99,000 units every six hours had proved un-

TABLE III

Total Dosage, Dosage Schedule, Blood Level Range and Organism Sensitivity to Bacitracin

No.	Total Dose (Units)	Dosage Schedule (Units q6h)	Bacitracin Blood Level Range	Bacitracin Sensitivity of Organism
1	1,803,000	76,000 50,000	0.24–1.30 0.06–0.75	0.02
2	495,000	33,000	0.09–0.24	0.02
3	908,000	76,000 38,000	0.5 0.3 –0.8	0.0062
4	1,398,000	76,000 38,000	2.0 1.5 –2.3	0.015
5	1,029,000	47,000	0.32–1.0	0.04
6	3,378,200	75,000 99,000	0.26–2.0 2.0	0.0075
7	570,000	76,000 38,000	0.8 0.35–0.66	0.01
8	700,000	50,000	0.2 –0.48	0.015
9	600,000	50,000	0.43–0.86	—
10	250,000	50,000	0.6 –1.0	0.004
11	1,200,000	50,000	0.2 –1.6	—
12	623,000	33,000 60,000	1.0 0.32–0.75	—
13	150,000	50,000	0.5 –0.66	0.13
14	2,654,000	33,000 66,000 99,000	0.08–0.48 0.09–0.5 1.3 –2.0	0.02

successful in sterilizing the blood stream, penicillin in massive doses (1,000,000 units every two hours), supplemented by caronamide, was given. Penicillin blood levels in excess of 10 units per c.c. were obtained, a thousand times the penicillin sensitivity of the infecting organism, but the patient died of heart failure on his thirty-second hospital day. An autopsy revealed that this was due to the erosion of an aortic valve cusp by a large vegetation.

Table 3 correlates the sensitivity of the infecting organism with the maximum level observed in the blood. It is apparent that in every instance

where recovery occurred the blood level was more than 10 times the sensitivity. In case 13 the blood level was 0.66 and the organism sensitivity was 0.13, only a five-fold difference. We are inclined to attribute failure in this case to inadequate blood levels of bacitracin.

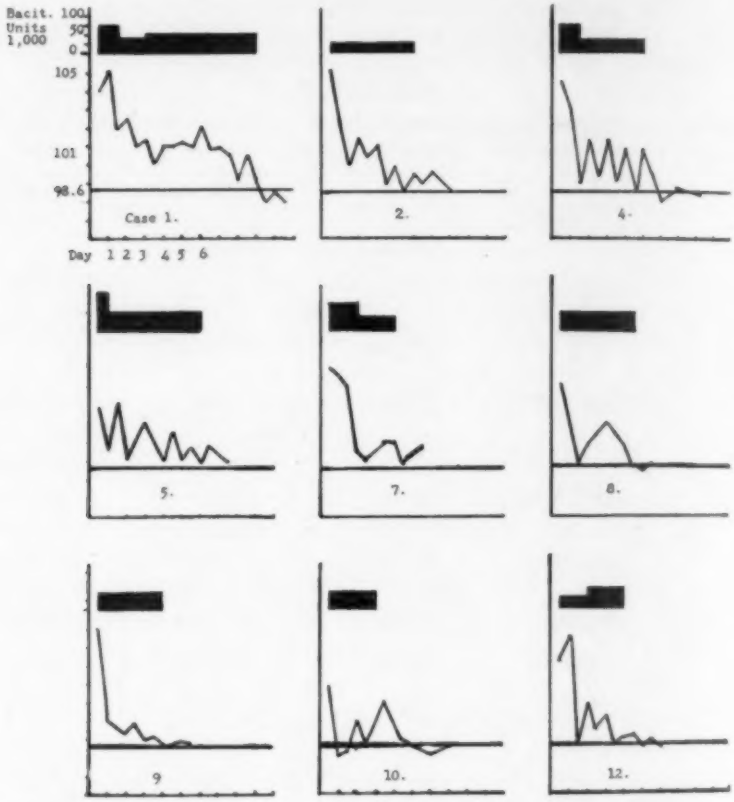

FIG. 1. Representative temperature curves of patients treated with bacitracin.

COMPLICATIONS

The only complication of pneumonia observed was pleural effusion, seen in two patients, in only one of whom was treatment for it required. Delirium tremens was present in five patients, and three had liver disease, probably secondary to long-standing alcoholism. One patient was pregnant and miscarried three weeks after recovery from the pneumonia. Two patients were infested with hookworms.

The clinical course in a complicated case is illustrated by case 6 (figure 3).

This patient was admitted to the hospital with a lobar pneumonia of the left lower lobe and bacteremia due to Pneumococcus Type II. For the first three days

he had delirium tremens and had to be physically restrained and heavily sedated. There was definite evidence of cirrhosis of the liver, and a history of previous lung infections and pleurisy. At the end of six days of 75,000 units of bacitracin every six hours his temperature was still high, and he had a large pleural effusion on the left side. This was tapped on the eighth day and 500 c.c. of purulent fluid (4,000 white blood cells per cu. mm.[3]) were removed. This fluid proved to be sterile on culture and had a bacitracin concentration of more than one unit per c.c. Ninety thousand

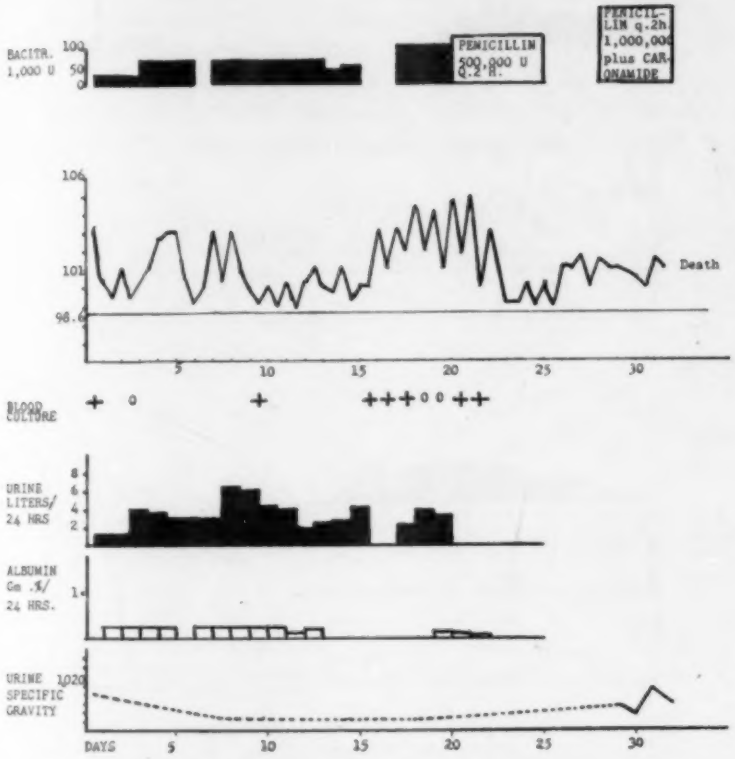

FIG. 2. Clinical course of a patient with pneumonia due to Pneumococcus II, complicated by acute bacterial endocarditis with fatal outcome.

units of bacitracin were instiiled directly into the pleural cavity. Following thoracentesis, the patient was subjectively improved but the temperature continued to be high and the dose of bacitracin was increased to 98,000 units every six hours. A chest tap two days later yielded only 50 c.c. of sterile fluid, with a cell count of 400 white blood cells per cu. mm.[3] Fifty thousand units of bacitracin were instilled intrapleurally. On the twelfth hospital day the temperature fell to 100° F. The chest roentgenogram at this time showed several pockets of fluid in the left pleural cavity and clearing of the underlying pneumonic process, so the drug was discontinued. For the next two weeks the temperature remained between 100 and 101° F., and the patient had a cough productive of tenacious, red-brown sputum. On the twenty-seventh hospital day, bacitracin by aerosol inhalation was begun, 10,000 units three times a day. The temperature dropped promptly and remained below 100° F., and the

cough and sputum decreased. The sputum became white and more fluid in character. The aerosol was continued for eight days and was discontinued at that time because of the appearance of an urticarial skin eruption on the arms and trunk. This disappeared two days after therapy was stopped. Roentgenograms of the chest now showed complete clearing of the lung fields except for residual pleural thickening. The patient was discharged to a convalescent home on the forty-eighth hospital day, after having received a total of 3,378,200 units of bacitracin.

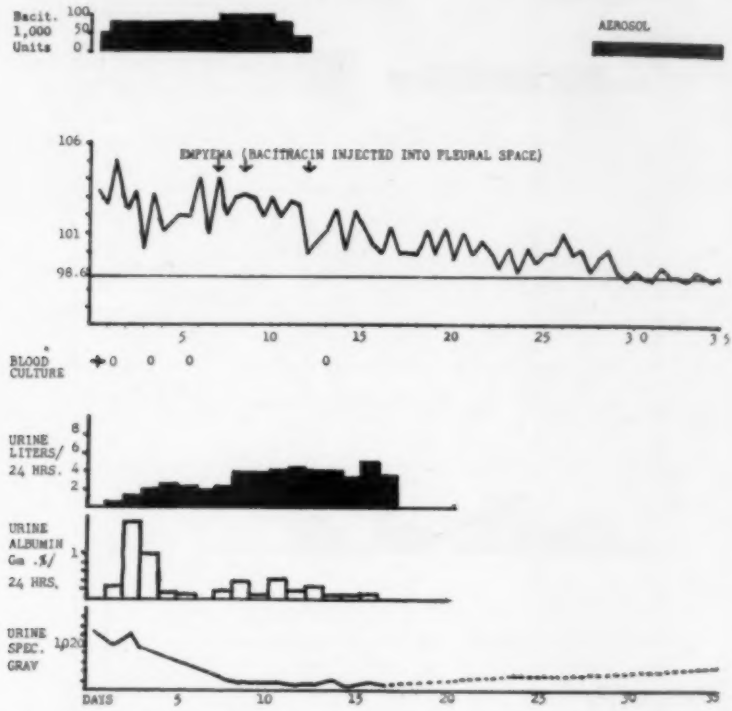

FIG. 3. Clinical course of pneumonia due to Pneumococcus II, complicated by bacteremia and empyema (case 6).

TOXICITY STUDIES

In the mouse [3] and, to a slight extent in monkeys,[4] bacitracin in large doses produces a degenerative lesion in the tubules of the kidney. The mouse is the only easily available laboratory animal susceptible to the nephrotoxic action of bacitracin. Careful studies on serially sacrificed mice show a lower nephron nephrosis which, if sufficiently severe, leads to an obstructive uropathy resulting in death.[9] Sublethal doses, however, leave little evidence of permanent damage in the kidneys when examined several months later. The LD_{50} (subcutaneously) for mice given the lots of bacitracin used in this study every six hours for five days is 250 units for a 20 gm. mouse. On a weight basis, this would be equivalent to 750,000 units every six hours in a 60 kg. man.

Man, however, appears to be more susceptible than any other mammal so far observed, in that doses of bacitracin as small as 7,500 units every 12 hours produce albuminuria and casts in the urine. These appear after from four to eight doses of the drug, and usually persist for several days. If therapy is prolonged, the amount of albuminuria and casts diminishes and may completely disappear under therapy. With higher doses, such as were employed in the present series, the albuminuria generally persisted for a few days after the completion of therapy.

In our patients, the chief manifestation of renal damage was a loss of concentrative ability. After two days of treatment, the renal output was markedly increased and the specific gravity of the urine was invariably low. In table 4 the 24 hour output volume can be seen to be markedly increased

TABLE IV

Urine and NPN Studies on Patients Treated with Bacitracin

No.	Sp. Grav. Range	24 Hr. Vol. Range (c.c.)	Albumin before Rx	Quant. Alb. (gm.%)* Range	Albuminuria Duration after Rx	NPN (mg.%) Range
1	1.003–15	1,300–4,000	1 plus	0.1 –0.25	0	30–28
2	1.010–15	2,300–3,200	1 plus	0 –0.2	0	25–30
3	1.008–20	1,700–4,500	1 plus	0.05–0.15	0	30–29
4	1.004–13	1,000–2,500	0	0.1 –0.4	2 days	30
5	1.010–16	1,500–3,000	0	0.05–0.45	1 day	29–30
6	1.003–26	1,500–5,200	4 plus	0.10–1.7	4 days	29–30
7	1.004–16	1,000–1,400	1 plus	0.2 –0.4	2 days	53–25
8	1.005–11	1,300–4,200	1 plus	0.15–0.25	3 days	28–30
9	1.010	2,700–3,300	1 plus	0.15–0.75	3 days	30
10	1.018	950–2,400	1 plus	0.15–0.20	2 days	29–32
11	1.004–07	2,600–3,000	2 plus	0.1 –0.5	4 days	26–30
12	1.026	2,000–4,200	0	0.15–0.25	2 days	30
13	1.006	1,500–2,200	0	0.1 –0.4	3 days	32–25
14	1.005–16	1,000–6,500	2 plus	0.1–0.25	Till death	30–25

* Normal urines may show as much as 0.15 gm.% of albumin in the 24 hr. specimen.

in nearly every instance. Concentration tests done at the end of treatment showed impaired function (table 5), which gradually returned over a period of several weeks.

No patients showed nitrogen retention as a result of treatment. In only one instance (case 7) was an elevated non-protein-nitrogen observed, and this was due to dehydration on admission, since the next determination after two days of the drug was normal.

The excretion of phenolsulfonphthalein is definitely impaired (table 5), but shows return to normal before the concentrative power. Pulaski has also observed this,[10] and he emphasized the importance of the impaired initial concentration of the dye in the 15 minute specimen.

In evaluating nephrotoxicity in these patients, it is well to bear in mind that pneumonia itself is accompanied by a toxic nephrosis, at times fairly extensive, and that diuresis is a frequent accompaniment of the onset of recovery from pneumonia. Most of our patients had a toxic albuminuria

before treatment was begun. The kidneys of our fatal case, and of two other cases of endocarditis that had received bacitracin in large doses, showed diffuse tubular necrosis. However, two of these patients had had large doses of streptomycin, a drug which will also cause tubular lesions.[11] We have not yet had a chance to observe the kidneys of human beings who had received no therapy but large doses of bacitracin. One patient (not in this series) who died of diabetic acidosis after having had only 75,000 units of bacitracin showed no significant renal changes on microscopic examination.

Case 6, who had 4 plus albuminuria to begin with, received over 3,000,000 units of bacitracin. He showed a steady decline during the first few days in the amount of albumin excreted and thereafter the urine contained only a trace of albumin for the remaining period of treatment. He also showed polyuria and low specific gravity, and no nitrogen retention. Three weeks after treatment he still showed impaired phthalein excretion (table 5), but 10 days later his test showed marked improvement, although the first specimen was still low. The abnormally high excretion value obtained is presumed to be due to his chronic liver disease. The concentrative power was still impaired a month after treatment.

TABLE V

PSP Excretion Tests and Pitressin or Volhard Concentration Tests Following the Completion of Bacitracin Therapy

No.	PSP Excretion Test	15′	30′	60′	120′	Total	Concent. 1 hr. 2 hrs.
1	4 days after Rx	15	10	5	25	55%	1.016–1.017
	12 days after Rx	15	25	10	10	60%	
6	3 wks. after Rx	—	15	30	20	65%	1.012–1.011
	4½ wks. after Rx	15	25	25	25	90%	1.013
7	10 days after Rx	25	10	5	5	45%	(Volhard) 1.010–1.016
8	5 days after Rx		10	10	5	25%	(Volhard) 1.008–1.010
	11 days after Rx	25	15	15	5	60%	(Volhard) 1.005–1.011
9	2 days after Rx	—	15	15	10	40%	(Volhard) 1.010 fixed
	8 days after Rx	10	15	5	5	35%	(Volhard) 1.008–1.012
11	1 wk. after Rx	30	25	15	5	85%	(Volhard) 1.002–1.006
	2 wks. after Rx	30	15	25	5	80%	1.012

Abnormally high values of PSP excretion in cases 6 and 11 are probably due to liver damage, of which both cases had other evidence, such as positive cephalin flocculation tests.

Other evidences of toxicity were slight. Case 6 had an urticarial skin eruption of the type seen frequently following the use of penicillin. Several patients complained of painful, swollen buttocks after repeated injections. In some instances, some lots of bacitracin seemed to produce a low febrile reaction an hour after injection. These effects, we believe, will be eliminated with further purification of the drug.

Comment

The results in these cases show that as a bactericidal agent in the treatment of pneumococcal pneumonia, bacitracin is an effective agent. If doses are employed large enough to give blood levels 10 times the sensitivity of the invading organism, recovery should follow. Bacitracin given parenterally can be recovered in high concentration in the pleural exudate, as shown by case 6.

At the present time, the nephrotoxicity of bacitracin precludes its use in preference to penicillin. We would not hesitate on that account, however, to use the drug in cases where there was a sensitive organism that did not respond to penicillin or other therapy. We would not recommend its use in cases with preëxisting parenchymatous renal disease, but we do not consider a toxic albuminuria a contraindication. None of our patients showed any permanent or serious damage to the kidneys, and the serial studies in mice show that nonlethal doses of bacitracin leave no permanent scars in the kidneys. In our opinion, bacitracin is only slightly more nephrotoxic than streptomycin.[11] This toxicity is probably due to the presence of d-amino acids in the bacitracin at present available. Studies are at present under way to devise means to remove or neutralize the effect of these elements in the drug.

Summary and Conclusions

1. Bacitracin, in doses of 30,000 to 99,000 units intramuscularly every six hours, was given to 14 patients with lobar pneumonia. Twelve patients recovered, one had to be changed to penicillin, and one patient died of bacterial endocarditis, although his pneumonia responded well to treatment.

2. It was observed that blood levels at least 10 times the sensitivity of the organism were obtained in the recovered cases.

3. Bacitracin is an effective agent in the treatment of pneumococcal pneumonia.

4. All patients exhibited moderate albuminuria, casts, and impairment of concentrative power of the kidney and of phenolsulfonphthalein excretion, lasting for a variable time after therapy. No elevation of non-protein-nitrogen was observed. This nephrotoxicity of bacitracin should excite caution, but does not contraindicate its use in suitable cases.

The bacitracin used in these studies was supplied by the Ben Venue Laboratories, Pittsburgh, Pa., and the Commercial Solvents Corporation, Terre Haute, Indiana.

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LIPEDEMA OF THE LEGS: A SYNDROME CHARACTERIZED BY FAT LEGS AND EDEMA *

By Lester E. Wold, M.D., Edgar A. Hines, Jr., M.D., F.A.C.P., and Edgar V. Allen, M.D., F.A.C.P., *Rochester, Minnesota*

There is little in the literature on abnormal localized depositions of body fat to clarify the syndrome of lipedema of the legs which two of us (E. V. A. and E. A. H.) described in 1940.[1] Confusion and uncertainty, both manifested in an extensive article by Lyon [2] in 1910, are demonstrated by the use of such terms as "oedeme hystérique" and "pseudo-edema." We are not concerned in this presentation with the type of lipodystrophy (lipodystrophia progressiva) which is generally felt to be characterized by loss of subcutaneous fat of the upper half of the body and increased deposition of fat in the buttocks and lower extremities.[3-6] As a digression, it is worthy of comment that steatopygia (fat buttocks) is considered a manifestation of beauty among the Hottentots.[7] The syndrome which we shall consider in this presentation is definitely not considered a manifestation of beauty in modern "civilized" living. Indeed, it is quite probable that much or all of the distress (both emotional and physical) associated with lipedema would not occur were "fat legs" considered a manifestation of beauty.

Description of the Syndrome "Lipedema"

The term "lipedema" is one which has been coined by two of us (E. V. A. and E. A. H.) to describe large legs due to the subcutaneous deposition of fat in the buttocks and lower extremities and the accumulation of fluid in the legs (figure 1). Characteristically, there is symmetrical bilateral enlargement of the buttocks and lower extremities which begins almost imperceptibly and progresses gradually. Progressive enlargement of the limbs is ordinarily associated with gain of weight, but evidence of obesity of the trunk, upper extremities, face and neck may be entirely absent; in some instances, there is generalized obesity. The enlargement of the limbs is accentuated by orthostatic activity, particularly in warm weather, and although rest in bed may cause some decrease in size of the limbs, owing to removal of fluid, even prolonged rest in bed will not cause the limbs to become normal in size. Episodes of inflammation, such as are commonly observed in lymphedema, are uniformly absent. The characteristics that distinguish lipedema from lymphedema are given in table 1.

The examination ordinarily discloses no abnormalities except those referable to the lower extremities. The legs and buttocks are symmetrically

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From the Mayo Foundation and the Division of Medicine of the Mayo Clinic, Rochester, Minnesota.

FIG. 1. Lipedema of the lower extremities of a woman aged 48 years. *a*. Anterior view. *b*. Posterior view.

enlarged owing to the subcutaneous deposition of fat. The feet are ordinarily normal in size and configuration (figure 2). There is moderate to great sensitiveness to digital pressure and, particularly at the end of the day, there may be some evidence of edema, although the evidence is not great enough to explain the patient's statement relative to the degree of swelling which has occurred as a result of orthostatic activity. The skin and subcutaneous fat are soft and pliable. There may be generalized obesity, but in most instances the upper parts of the body are "normal" in size and contour.

Patients with lipedema complain of enlargement of the limbs, aching distress in them, particularly during activity, and rather marked tenderness

TABLE I

Differential Diagnosis

Characteristics	Lipedema	Lymphedema
Sex	Women (almost exclusively)	Men and women
Obesity	Present	Present or absent
Region involved	Always both limbs	Usually one limb
Symmetry	Always	Very seldom
Pain on pressure	Usually present	Usually absent
Progression	All parts of limb are involved simultaneously	From distal portion of limb, proximally
History of episodes of acute cellulitis	Absent	Occasionally present
Nature of swelling	Usually soft	Usually firm
Pitting edema	Usually minimal	Usually marked
Effect of elevation	Persistent enlargement	Reduction to normal size in early stages
Family history of large legs	Frequently obtained	Almost always not obtained

of the legs; the last can be easily demonstrated by digital pressure. The emotional reaction of patients to this syndrome varies from curiosity relative to its significance to marked evidence of anxiety and tension. In its most florid form there are exhaustion, insomnia, nervousness, tenseness, melancholia, anxiety and feelings of frustration. Patients are ordinarily ashamed of their legs or feel that their large legs have "ruined my life." These feelings and symptoms are understandable reactions to a situation which is in conflict with the great premium ordinarily attributed to comely

FIG. 2. Mild lipedema of the lower extremities of a woman aged 46 years. There is no lipedema of the feet where pressure has been maintained by shoes.

legs. Patients with lipedema are ordinarily very sensitive about the appearance of their legs; they wear long skirts, avoid appearance in swimming suits and stand behind chairs at parties. They are likely to be "mirror peepers," searching repeatedly in mirrors for evidence that the appearance of their legs is not actually as bad as it seems to be. Quite characteristically, they examine visually the legs of other women, hoping, it seems, to be comforted by finding someone with legs as homely as theirs.

The basic difficulty in lipedema is the subcutaneous deposition of fat,

the cause for which remains obscure. The situation differs from ordinary obesity both in the distribution of fat and in repeated observation by patients that a low caloric intake causes diminution of subcutaneous fat in the upper part of the body but has little influence on the lower extremities. We have not actually confirmed this opinion by direct observation. Because fat is a poor supporting structure, lacking firmness, it offers little resistance to the passage of fluid from the blood vessels into the tissue spaces; hence, the large limbs become even larger when patients are active on their feet.

It is interesting to speculate on the reasons why these patients usually have no excess accumulation of fat or of edema in the feet. This is due most likely to the continued external pressure on the tissues from tightly fitting shoes. In one patient who had worn old-fashioned high shoes for many years, the excess fat accumulation and the edema were not present beneath the areas covered by the shoes.

The treatment of lipedema is usually unsatisfactory. In cases of generalized obesity, sharp reduction of weight may help. In cases of obesity affecting only the region below the waist, reduction of weight may cause but little reduction of the localized obesity. The restriction of fluids and the use of diuretics such as potassium nitrate are usually without benefit. Heat and gentle massage may relieve the distress. If activity on the feet causes much accentuation of swelling, elastic stockings may be tried, but the discomfort caused by them frequently exceeds the benefit realized from their use. Reassurance that the condition is not hazardous to health or to life is important. Particularly is it important to inform the patient that "Bright's disease" and heart disease are absent. If the assumption is correct that lipedema of the feet is prevented by the pressure from shoes, the early use of adequate elastic supports on the legs might prevent the development of marked enlargement of the legs. A sympathetic discussion of the nature of the condition with the patient and an explanation of the physiologic basis are usually helpful. A kindly presentation of the probability that the patient may need to accept the situation, and encouragement of the patient to readjust her life and reactions to an unavoidable situation and to live normally, may give her courage to do so. More formal psychiatric care may be necessary. In some instances, plastic surgical procedures may be of benefit.

Report of Cases

This is a study of 119 cases of lipedema in patients examined at the Mayo Clinic from 1937 through 1946. Each patient was examined by one of the consultants in the section on peripheral vascular diseases of the clinic. The same diagnostic criteria were satisfied in each case. The following features of the clinical syndrome were evaluated:

Family History and Nationality. Nineteen of the 119 patients (16 per cent) gave a history of similar "large legs" in female members of their family. The one man in the series presented such a history. Because of the rather

strong family history, and because it was felt that lipedema might represent a peculiar type of body build common to some race (as steatopygia is common among Bushfolk and Hottentots), the nationality, race or place of birth of each patient was noted. The distribution, which roughly corresponds to the cross section of all patients seen at the clinic, is as follows: American, 55; British Isles, 16; Jewish, 16; North Europe, 15; Scandinavia, 7; Canadian, 4; East Europe, 3; South Europe, 2; Negro, 1.

Sex. Only one of the 119 patients who had lipedema was a man. He was 36 years of age and weighed 233 pounds (about 106 kg.). He had noted bilateral swelling of both lower extremities for one year prior to registration. He stated that bilateral ligation of the saphenous veins and injection therapy for varicose veins had been performed. When he was seen at the clinic, obesity of the legs and buttocks was prominent. Minimal varicosities were present. There was no pitting edema. The patient stated that female members of his family had similar-appearing "fat legs."

TABLE II

Lipedema Among 119 Patients

Age at which increase in size of legs was first noted, years*	Patients
Childhood (to 10 years)	8
11 to 20	16
21 to 30	19
31 to 40	23
41 to 50	26
51 to 60	12
61 to 70	6
71 to 80	1
Unknown	8
Weight, pounds†	**Patients**
101 to 120	14
121 to 140	31
141 to 160	35
161 to 180	15
181 to 200	10
201 to 220	6
221 to 240	5
More than 240	3

* Youngest patient 8 years; oldest 71 years. One patient stated onset "in infancy," another "as a girl," and several stated they had "always" had large legs.

† Lowest weight 103 pounds; highest 275 pounds.

Age of Onset. The age of onset of the increase in size of the legs was determined from the history (table 2). In most instances a definite age of onset was not noted on the history but was calculated from the patient's statement as to the duration of the enlargement, which in many instances was at best a rough approximation. A study of the table indicates no greater frequency of onset during the decades embracing the menarche or menopause than in other decades.

Pain. Forty-eight of the patients (40 per cent) complained of pain in the lower extremities. It was commonly described as an ache which was constant or which occurred only while the patients were on their feet for substantial periods of time. The distress involved the legs below the knees and, occasionally, the feet. Tenderness was common.

Obesity and Body Build. Fourteen patients weighed less than 120 pounds (about 54 kg.), and two patients weighed more than 270 pounds (about 122 kg.). Table 2 shows the distribution of the 119 patients according to weight, and demonstrates that overweight may or may not be present. Specific mention of prominent malleolar fat pads was made in 17 instances. Occasional mention was made that the large legs had been first noted with the onset of generalized obesity. Frequent mention was made that moderate reduction of weight had had no effect on the apparent size of the hips or extremities.

Fifty consecutive patients were studied in an attempt to get an idea of the general body build by correlating the height of the individual with her weight. The mean height in this study was 63 inches (about 160 cm.), and the mean weight was 151 pounds (about 68 kg.). This would suggest that this group was of the sthenic type of body build.

Presence of Pitting Edema. Twenty-eight of the 119 patients (24 per cent) had minimal to mild pitting edema. Eleven of the patients aggravated, only during warm summer months.
volunteered the information that the swelling of their legs was present, or

Presence of Varicose Veins. Forty-two (35 per cent) of the patients had varicose veins. In almost all instances these varicosities were minimal. Only three patients presented ulcers of chronic venous insufficiency. Two patients had had previous injection treatment for varicose veins. Incompetent varicose veins in the greater or lesser saphenous systems were noted in 11 patients (9 per cent). In nine of these 11 patients the incompetency was designated as being in the greater saphenous vein.

History of Thrombophlebitis. Twelve of the patients (10 per cent) related a history of previous thrombophlebitis and six (5 per cent) presented areas of chronic indurated cellulitis. The indurated cellulitis was considered a complication of the associated chronic venous insufficiency and not of the lipedema.

Basal Metabolic Rate. Basal metabolic determinations were made in 30 of the 119 patients. In 27 of these 30 instances, the basal metabolic rate was less than 0 per cent, that is, between minus 1 and minus 22 per cent. None of these patients had clinical evidence of myxedema. In only three instances was the basal metabolic rate elevated. The basal metabolic rate of one patient who had exophthalmic goiter was plus 40 per cent. Another patient had an adenomatous goiter with hyperthyroidism; the basal metabolic rate was plus 20 per cent. The third patient had a basal rate of plus 16 per cent without clinical evidence of hyperthyroidism.

Accuracy of Diagnosis. Thirty-seven of the 119 patients were seen originally by consultants particularly skilled in peripheral circulatory disturbances. In 17 of the remaining 82 cases the diagnosis was correctly made by consultants in other diagnostic sections of the clinic. The tentative diagnoses that had been noted prior to examination by one of the consultants in the peripheral vascular section were as follows in 65 instances: lymphedema, 19; venous insufficiency with obesity, 11; lymphedema praecox, five; lymphedema or lipedema, five; "swollen" legs, five; lipodystrophy, four; venous insufficiency, four; obesity, three; edema, three; Milroy's disease, two; no diagnosis, two; lymphedema with adiposity, one; old leg injury, one.

These diagnoses indicate the frequency with which the syndrome of lipedema is confused with vascular disease affecting the lower extremities, especially lymphedema or venous insufficiency. If one keeps in mind the clinical features of lipedema, such errors in diagnosis should occur less frequently.

Associated Neurosis. Thirty-four of the 119 patients (29 per cent) were concerned about their "large legs" to the extent that actual neurosis had developed. This group typically was either very sensitive about the appearance of their legs, or interpreted the enlargement to be evidence of some grave disease.

Summary

Lipedema of the legs is a syndrome characterized by fat legs and orthostatic edema. A clinical evaluation of 119 patients with lipedema has been presented. The condition is often confused with vascular diseases affecting the lower extremities, especially chronic venous insufficiency and lymphedema.

Of the 119 patients, all but one were women. A similar condition often occurs in other members of the family. The majority of the patients were overweight, a preponderance of the excess fat being in the lower half of the body. In most instances this represented an exaggeration of the normal female configuration.

The age at which an increase in the size of the legs was first noted could not be accurately determined, but there was apparently no greater frequency of onset during the decades of the menarche or menopause than in other decades.

Discomfort in the legs, consisting of diffuse pain, tenderness and aching distress, was a prominent symptom in about one-half of the group.

Chronic indurated cellulitis and stasis lesions did not occur unless there was an associated, coincidental chronic venous insufficiency. The basal metabolic rate was usually less than 0 per cent, but none of the group had clinical evidence of myxedema.

Mild to marked anxiety concerning the appearance of the lower extremities and possible serious significance of the edema was usual. About one-third of the patients presented evidence of neurosis.

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CASE REPORTS

THE ANEMIA OF MYXEDEMA, WITH SPECIAL REFERENCE TO PERNICIOUS ANEMIA *

By MAURICE E. LEONARD, M.D., ERNEST H. FALCONER, M.D., F.A.C.P., and MATTHEW J. ELLENHORN, M.D., *San Francisco, California*

THE co-existence of myxedema and anemia in the same patient has been recognized for over 60 years.[1, 2, 3] This relationship is emphasized in numerous reports which confirm the finding that anemia occurs in from 50 to 60 per cent of patients with myxedema.[4, 5, 6, 7] The anemia is usually of moderate degree; hemoglobin values of less than 50 per cent and red blood cell counts below 3 million per cu. mm. are rarely found. Normocytic normochromic, normocytic hypochromic and macrocytic hyperchromic blood pictures have been described [4, 5, 6, 7, 8, 9, 10, 11] (table 1). This lack of uniformity in the blood picture is difficult to reconcile with a common etiologic factor, unless one postulates that influences

TABLE I

Types of Anemia Associated with Myxedema

Authors	Macrocytic Hyperchromic Anemia	Normocytic Normochromic Anemia	Normocytic Hypochromic Anemia	Total
Baldridge and Greene[17]	3	2	6	11
Bomford[10]	5	0	5	10
Emery[7]	4	1	6	11
Holbøll[21]	5	14	9	28
Stern and Altschule[14]	7	9	1	17
Stone[8]	5	0	18	23
Total	29	26	45	100

other than pure thyroid hypofunction may play a rôle. This postulation is borne out in some instances by failure of the anemia to respond to specific thyroid therapy unless iron, liver principle or certain endocrine substances are employed.[12, 13]

Excluding certain modifying conditions, as iron deficiency, chronic blood loss, infections and lack of liver principle, there remains an appreciable number of patients in whom myxedema appears to be the sole cause of the anemia. In spite of the variations in the types of anemia which have been reported in myxedema (table 1), experimental evidence, both in animals and in human beings, indicates that the characteristic anemia of myxedema is of the macrocytic type. This is shown by blood changes following thyroidectomy [13, 14, 15] and their reversal fol-

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lowing the administration of thyroid extract. The mechanism which produces the anemia is not clear. It was once believed that thyroxin is necessary for normal hematopoiesis,[22] an hypothesis based on the tenuous evidence that deficiency of thyroxin is sometimes associated with anemia. Actually, anemia does not occur in all cases of myxedema, nor is there any correlation between the severity of anemia when present and the degree of hypometabolism as shown by the clinical features of the disease and the basal metabolic rate. Bomford[10] suggested that deficiency of thyroxin affects hematopoiesis only indirectly, by reducing the oxygen consumption of the tissues; therefore, the reduction in the number of oxygen carriers is merely a physiologic adaptation.

Of special interest is the occasional association of myxedema with a clinical picture resembling pernicious anemia. This anemia is not the simple macrocytic type referred to above but a marked anemia in conjunction with leukopenia, yellowish pallor of the skin, glossitis, paresthesias, and frequently achylia gastrica. In some of the reported cases[8, 9, 17] the anemia was corrected with liver principle alone, while in others therapeutic response failed until a sufficient quantity of thyroid substance was supplied.[17] It should be emphasized that a number of the patients who failed to respond favorably to liver therapy were treated with liver extract in quantities that today would be regarded as inadequate.

It has not been established whether myxedema and pernicious anemia are causally related or whether their concurrence is merely coincidental. That the two diseases may occur independently in the same individual is not surprising. No available statistical data exist which might indicate whether the incidence of pernicious anemia is higher in patients with myxedema than in the population at large. An interesting fact is the frequency of achlorhydria in patients with myxedema. Lerman and Means[18] demonstrated that 53 per cent of their patients with myxedema had complete achlorhydria. When correction is made for age, this figure still represents a very high incidence. It is surprising that so little information is available regarding the bone marrow in myxedema. The studies that have been published show a quantitative reduction in the amount of functioning marrow[19, 20] but no striking qualitative alterations. We are unaware of any instance where megaloblastic transformation of the bone marrow has been described.

The authors have had the opportunity of observing a patient over a period of years in whom myxedema and anemia co-existed. They consider the hematologic features to be of sufficient interest to warrant a detailed case report.

Case Report

A white female* was first seen in the Outpatient Clinic of the University of California Hospital in 1924, at the age of 30 years. At that time she complained of abdominal pain, constipation, weakness, dizziness, occasional vomiting and attacks of syncope. Physical examination showed bradycardia, enlargement of lymph nodes of the neck and groins, slight edema of the ankles, and tenderness over the epigastrium. The urine contained many pus cells and bacteria. A blood count showed 67 per cent hemoglobin and 2.73 million erythrocytes. Gastric analysis (without histamine) revealed 8 units free and 23 units of combined acid. Kolmer and Kahn were negative.

*Some of the endocrinologic and hematologic features of this case were originally reported by Lisser, H., and Anderson, E. M.: Three cases of adult myxedema in women, reported for the purpose of calling attention to their widely different symptomatology and clinical findings, Endocrinology **15**: 365–381, 1931.

A gastrointestinal series showed no abnormalities. A chest film showed obliteration of the right costophrenic angle, presumably from an old pleurisy. The basal metabolic rate was minus 33 per cent. The diagnosis was "myxedema with secondary anemia." Treatment consisted of the administration of 4 gr. thyroid extract daily.

By January, 1925, the patient was much improved. Her basal metabolic rate was minus 6.5 per cent, hemoglobin 75 per cent,* erythrocytes 4.08 million, and leukocytes 6,900. Thyroid dosage was reduced to 2 gr. daily. A few months later the patient complained of chest pain, abdominal discomfort and dizziness. An electrocardiogram was interpreted as consistent with myxedema. The basal metabolic rate at this time was plus 7.9 per cent. Examination of the blood disclosed hypochromia of the red cells.

For the next three years the patient continued to attend various clinics because of multiple complaints. During this period she took thyroid sporadically. Her basal metabolic rate remained within normal range. A second gastric analysis showed complete achlorhydria. Occasionally the blood showed a moderate normocytic, normochromic anemia and slight leukopenia. Five years later her blood contained 78 per cent hemoglobin, 4.43 million erythrocytes and 13,900 leukocytes. At about this time she became careless in the regularity of her medication. In October, 1930, the basal metabolic rate was minus 21 per cent. The blood contained 78 per cent hemoglobin (10.7 gm.) and 3.8 million erythrocytes; a smear showed macrocytes. Because of the change in the blood picture to a macrocytic type, and the presence of achlorhydria, the possibility of pernicious anemia was considered. However, on increased thyroid administration alone the blood level increased slowly, so that by August, 1932, a count showed 87 per cent hemoglobin (12 gm.), 4.12 million erythrocytes and 6,480 leukocytes.

Apparently there was remission of all symptoms, as the patient did not return to the clinic for nearly two years, until March, 1934, when she again reported with complaints of weakness, ankle edema, dyspnea and nervousness. The blood level was down to 70 per cent hemoglobin (9.7 gm.) and 2.9 million erythrocytes; many macrocytes were found in a stained smear. The basal metabolic rate was plus 1 per cent. A barium meal examination showed a normal gastrointestinal tract. A diagnosis of pernicious anemia was made, and the patient was transferred to the hematology clinic.

From June, 1934, to May, 1936, the patient attended the blood clinic regularly. Therapy consisted of parenteral liver extract at weekly intervals, thyroid extract, 2 to 3 gr. daily, and iron and ammonium citrates, 6 gm. daily. There was a slow but steady rise in blood level, but it was not until May, 1936, that the blood became normocytic and normochromic. The count at this time showed 88 per cent hemoglobin (12 gm.), 4.43 million erythrocytes and 5,590 leukocytes. The basal metabolic rate was minus 9 per cent; gastric analysis showed no free HCl after histamine. The patient felt quite well and was working steadily. By September, 1937, the blood level was 90 per cent hemoglobin (12.4 gm.), 5.11 million erythrocytes and 10,000 leukocytes.

In the latter part of 1937 the patient began to complain of attacks of sharp pain in the lower abdomen, radiating along the course of the ureters. Urologic investigation disclosed a bilateral nephroptosis and pyelitis on the right. In March, 1938, a bilateral nephropexy was performed, after which the urinary tract symptoms abated. In spite of the renal infection the blood level was well maintained. A blood count shortly after the operation showed 94 per cent hemoglobin (13 gm.), 4.4 million erythrocytes and 5,750 leukocytes.

* Because the Sahli colorimetric scale was used in the patient's earlier blood studies, the authors believe that the recorded hemoglobin values from 1924 to 1933 err on the low side.

The patient continued to receive liver extract at regular intervals but, unknown to the clinician, had ceased taking thyroid "because it made her nervous." In September, 1938, she complained of weight gain, a feeling of cold and swelling of her ankles. A basal metabolic rate taken at this time was minus 25 per cent. The blood had again become macrocytic and hyperchromic. Thyroid medication was resumed, together with 15 units of liver extract every three weeks. In December, 1938, the blood level was 86 per cent hemoglobin (11.9 gm.), 3.59 million erythrocytes and 4,160 leukocytes.

For the next three years the patient reported rather irregularly. She stated that she was taking 2 gr. thyroid extract daily. She received liver extract when she reported, but there were periods of two to three months when she did not come to the clinic. During October, 1941, she complained of severe retrosternal pain on exertion. Physical and electrocardiographic examinations revealed no significant findings. The blood contained 80 per cent hemoglobin (11 gm.), 3.36 million erythrocytes and 5,500 leukocytes. Parenteral liver was increased to one injection of 10 U.S.P. units per week. On this régime the blood level rose and the chest pain abated, but now a new train of symptoms appeared. These consisted of hot flashes, dizziness, urinary frequency and irregular menses. The patient was referred to the gynecologic clinic with a diagnosis of menopausal syndrome. During 1942 and 1943 she was treated with estrogens at the women's clinic. The results were apparently satisfactory. Because she rarely reported to the hematologic clinic, she received no liver therapy after February, 1942. Nevertheless, the blood level remained high. A count taken in May, 1943, showed 90 per cent hemoglobin (12.4 gm.), 4.85 million erythrocytes and 6,800 leukocytes.

In 1944 the patient moved from San Francisco to a sparsely populated rural area. For the next two years she received practically no liver therapy, although she continued to take from 1 to 3 gr. thyroid extract daily. On her infrequent visits to the clinic, blood counts showed that she was maintaining her hemoglobin and red cell level within a normal range. She was next seen in February, 1944, because of rectal bleeding and hemorrhoids. The hemoglobin had dropped to 70 per cent (9.6 gm.) and the red blood cells to 3.95 million. Ferrous sulfate, 0.9 gm. daily, was administered, and the hemorrhoids were treated. Shortly thereafter bleeding ceased. By May, 1945, the hemoglobin had increased to 90 per cent (12.4 gm.) and the erythrocytes to 4.29 million. At this time there was grave doubt as to the validity of the diagnosis of pernicious anemia. Therapy had been very inadequate for nearly two years, yet there was no significant drop in hemoglobin or red blood cells, and no gastrointestinal or neurologic signs had developed. The one episode of anemia could be accounted for by loss of blood, and the condition had responded promptly to iron. Therefore, when the patient reported to the clinic a month later with a complaint of extreme fatigue, it was disturbing to find that she had a marked hyperchromic, macrocytic anemia (figure 1). The anemia responded promptly to parenteral liver therapy. In September, 1945, the patient's blood contained 94 per cent hemoglobin (13 gm.) and 4.35 million red cells; the sternal marrow appeared normal.

The patient was not seen again until August, 1947. She had been very negligent regarding treatment. As there were no symptoms or detectable blood abnormality at that time, it was decided to refrain from liver therapy and observe any changes in the blood level. The patient was advised to continue with thyroid and to report to the clinic regularly for blood counts. Under this régime she remained in good health until November, 1948, when she began to complain of retrosternal pain, extreme weakness and fatigue. The hemoglobin had decreased to 72 per cent (10 gm.), and the red cells numbered only 2.32 million. A sternal puncture study showed an erythroblastic marrow (table 2). Examination of the gastrointestinal tract with

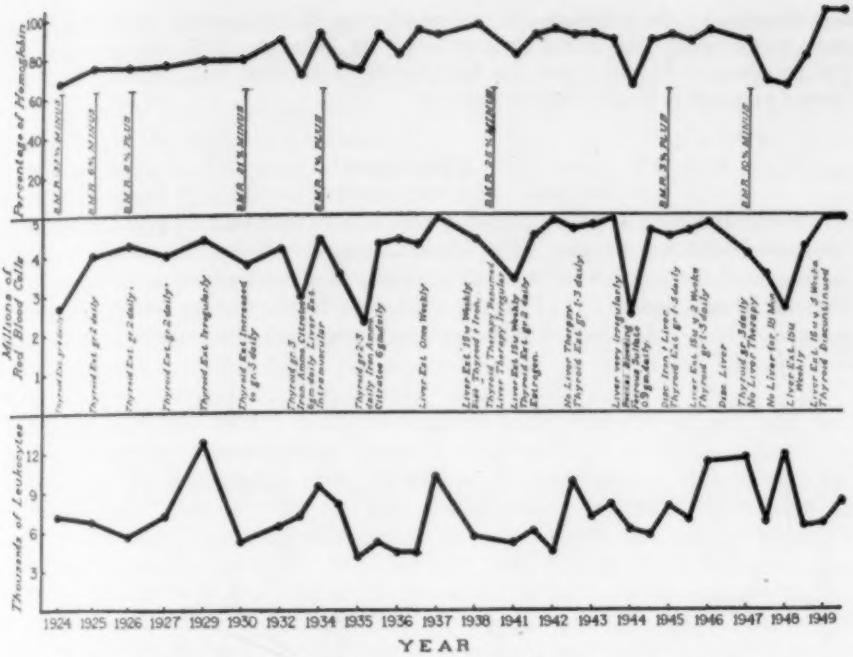

FIG. 1. Fluctuations in hemoglobin and erythrocytes over a 25 year period.

barium showed slight atrophic changes involving the superior portion of the stomach, with no further roentgenologic evidence of disease.

Institution of liver therapy was followed by a prompt reticulocytosis. Six days after the initial injection, 25 per cent of the red cells were reticulocytes. One month later the hemoglobin had increased to 88 per cent (10.8 gm.) and the red blood cells

TABLE II

Differential Count on Sternal Bone Marrow

	4-30-48	11-17-48	7-18-49
Myeloblasts	0	0	1.6
Promyelocytes	0.8	0.2	2.0
Myelocytes { neutrophils	7.2	5.2	10.0
Myelocytes { eosinophils	3.2	0.8	0.8
Metamyelocytes	3.8	7.2	18.8
Nonsegmented neutrophils	20.2	4.8	11.2
Segmented neutrophils	1.0	4.4	22.4
Eosinophils	1.2	0.4	0.8
Lymphocytes	2.0	1.0	13.2
Monocytes	0	0.5	0
Plasma cells	6.8	0.2	0.8
Reticuloendothelial cells	1.0	0	0
Megakaryocytes	0.8	0	0.4
Megaloblasts	1.6	2.0	0
Pronormoblasts	12.2	22.4	2.8
Normoblasts	33.2	50.9	15.2
Mitoses	5.0	0	0

to 4.10 million. On a dosage schedule of 15 units of liver extract every three weeks, there was a steady rise in the blood values. By February, 1949, the hemoglobin was 102 per cent (14.1 gm.) and the erythrocytes numbered 5.10 million. The retrosternal pain and weakness had disappeared.

Discussion

When first seen at the age of 30 years, this patient had a fairly severe anemia associated with myxedema. The clinical response to thyroid extract was satisfactory, and the blood level was subsequently well maintained at a slightly hypochromic level (figure 1). For the next decade there were minor hematologic relapses which coincided with the patient's negligence in regard to her thyroid

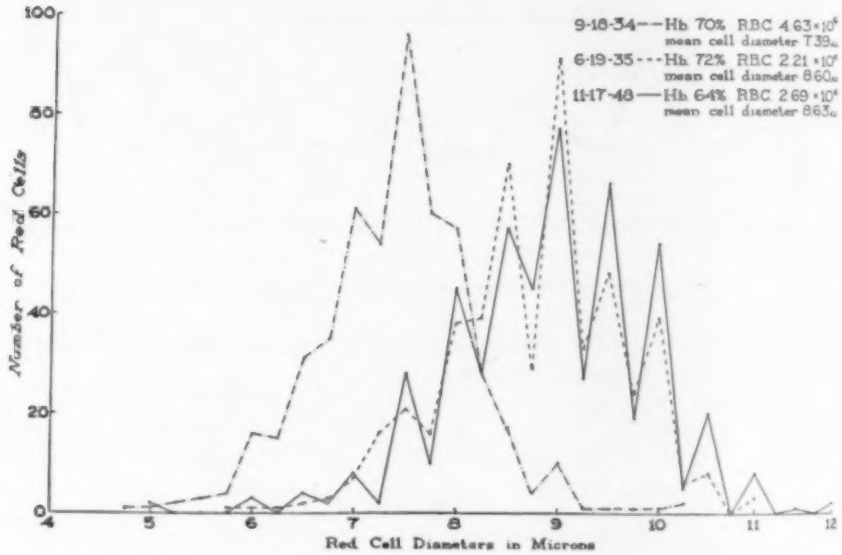

Fig. 2. Price-Jones curves illustrating change from normocytic to macrocytic anemia.

intake. Throughout this period the hemoglobin content tended to lag. The red cell count rose, and a Price-Jones curve (figure 2) showed a normal red cell diameter with a normal distribution about the mean.

Ten years after the inception of treatment, there occurred a serious hematologic relapse which could not be related to myxedema. It coincided with a marked change in the character of the erythrocytes, which now became macrocytic. The Price-Jones curve (figure 2) showed the skewness characteristically seen in pernicious anemia, and the mean cell diameter had shifted considerably to the right. The diagnosis of pernicious anemia was considered at that time. Under a régime of combined thyroid and liver therapy, normal blood values were again restored, but only after two years of intensive treatment.

For the next 11 years treatment was not carried out as planned. There were two periods, one of two years' and the other of three years' duration, when the

patient received practically no liver extract. Despite this there were only two hematologic relapses, the first coinciding with a drop in the basal metabolic rate to minus 25 per cent, and the second with rectal bleeding. The former responded readily to thyroid medication and the latter to iron. In view of the patient's ability to maintain a satisfactory blood level for so long a period (with the two exceptions mentioned above) and with obviously inadequate therapy, the validity of the diagnosis of pernicious anemia was doubted.

Exactly 24 years after the presence of anemia had been first detected, the patient suffered a severe and dramatic hematologic relapse. A marked macrocytosis was again encountered (figure 2). A study of the aspirated bone marrow indicated a marked hyperplasia of erythropoietic elements (table 2). Megaloblasts were present but not in large numbers. Nevertheless, the response to liver principle was excellent; within a short time the peripheral blood picture and the marrow were restored to normal (figure 1, table 2).

It was not quite certain from the data at hand that the patient had both pernicious anemia and myxedema anemia, requiring liver principle and thyroid extract for normal hematopoiesis. Within a 25 year period, this patient exhibited in turn the three types of blood change which frequently have been associated with myxedema: a moderate macrocytic anemia due to myxedema; a hypochromic anemia secondary to blood loss, and, finally, a pernicious anemia caused by lack of liver principle. The transition from a simple macrocytic to a true pernicious anemia is predicated on the appearance of megaloblasts in the bone marrow, the disappearance of free hydrochloric acid from the gastric secretions, the change in the shape of the Price-Jones curve and, finally, in the excellent response to liver therapy. It is the opinion of the authors that we possess sufficient data in this case to satisfy the criteria deemed necessary to substantiate a diagnosis of true Addisonian pernicious anemia. From the data at hand we are not certain whether at present this patient could be maintained at a normal blood level on either parenteral liver or B_{12} therapy alone. Efforts to withdraw thyroid have not been successful, as the patient will not coöperate by stopping thyroid therapy for sufficient time to allow us to collect the necessary data. She claims her general body tone and strength deteriorate rapidly, and she has less ability to work when thyroid substance is withdrawn. We interpret the available data in our records thus: this patient has two deficiency states, lack of sufficient thyroid secretion, and lack of sufficient intrinsic factor to maturate the erythrocytes in her bone marrow. If this interpretation is correct, she needs both thyroid substance and erythrocyte maturing factor for the maintenance of her blood at the normal level.

Summary and Conclusions

1. A case of myxedema with clinical and laboratory findings covering a period of 25 years is presented in detail.

2. During this period the patient had an anemia of the macrocytic type associated with myxedema. There were intervals during which, due to blood loss, the picture assumed the characteristics of a hypochromic anemia.

3. The data gathered during the 25-year period are reported because they reflect gradual changes in the patient's systemic state, culminating in the addition of another disease entity: pernicious anemia.

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SPONTANEOUS RUPTURE OF THE ESOPHAGUS: REPORT OF TWO CASES *

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THE designation of spontaneous rupture of the esophagus has been given to an esophageal rent which could not be explained by preëxisting pathology such as congenital anomalies, inflammation, trauma, neoplasmas, diverticuli, ulcera-

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tions in esophageal or ectopic gastric mucosa, or aneurysms. As judged by the number of cases in the literature, the occurrence of spontaneous rupture is exceedingly rare. Since the first case was described by Boerhaave in 1724, approximately 70 have been reported. Within the last few years, however, attention has been focused on this syndrome, more cases have been recognized, excellent reviews by Barrett,[1] Eliason and Welty,[6] and Kinsella et al.[10] have appeared, and the hopeless prognosis recorded by Eliason and Welty as late as 1946 has been altered by the papers of Barrett,[2] and Olsen and Clagett,[14] describing the gratifying results of prompt diagnosis and adequate surgical treatment. It is now generally agreed that a patient with a ruptured esophagus is an emergency problem and that a prompt diagnosis is vital.

With the hope of increasing the awareness of this entity, and because of its rarity, the following cases are presented.

Case Reports

Case 1. A 33 year old white male was admitted to the hospital with the chief complaint of upper abdominal pain of approximately 12 hours' duration. During the previous evening he had been drinking heavily, and subsequently he vomited material that was described as being coffee-ground in nature. Following this episode of vomiting, he fell into a stuporous sleep and, upon awakening on the day of admission, was aware of a vague sense of abdominal discomfort. This discomfort became progressively more severe, and at 6 p.m. he collapsed at home. A local physician was called who administered pantopon at 8 p.m., with little relief. There was no previous history of gastric pain, dyspepsia, hematemesis or melena. Examination on admission at 9 p.m. revealed the patient to be in a shocklike state, with a clammy wet skin, a blood pressure of 90 mm. Hg systolic and 60 mm. diastolic, and a peripheral pulse of 150. The heart sounds were normal and the rate was rapid. Respirations were splinted. The lungs were clear to percussion and auscultation. A boardlike rigidity of the abdomen was noted, although tenderness was not marked. While the patient was in the emergency room, a gastric tube was passed and 50 c.c. of bright red blood were aspirated. The impression at that time was perforated peptic ulcer complicated by hemorrhage from an adjacent ulcer or concomitant gastritis.

An electrocardiogram disclosed only a sinus tachycardia at a rate of 148. A portable roentgenogram of the abdomen in the left lateral recumbent position did not reveal any free gas. On admission, the white blood count was 18,000 cells per cu. mm. with 83 per cent neutrophils, and the hematocrit was 37 mm.

In spite of the general impression that this was a surgical abdomen, operation was deferred because of the severe peripheral circulatory collapse. During the night 2,000 c.c. of whole blood were given, and other supportive measures, including nasal oxygen, penicillin and intravenous sulfadiazine, were employed. Despite these measures, however, the patient was comatose on the morning of the second hospital day, the blood pressure had dropped to 60 mm. Hg systolic and 40 mm. diastolic, respirations were rapid and cyanosis was marked. Death occurred 16 hours after admission.

At autopsy the abdomen was found to be entirely negative. There was no evidence of a ruptured viscus or of peritoneal irritation. When the chest plate was removed, however, the mediastinum was seen to be dark brown in color, and in the left pleural cavity there were 2,000 c.c. of dark brown fluid in which could be found undigested food particles. In the right pleural cavity 1,000 c.c. of similar fluid were present. No foreign body was detected. There was a semi-membranous, soft, grayish-black deposit in the posterior mediastinum around the esophagus, adherent to both mediastinal pleura, the continuity of which had been disrupted bilaterally.

The lungs grossly and microscopically were atelectatic and congested, and a fibrinous pleuritis was present. Upon opening the esophagus, a 3.5 cm. rent was found immediately above the diaphragm on the left posterolateral surface (figure 1). The surrounding mucosa was smooth and gray, and the edges were sharply demarcated. About the external surface of this rent, the membranous, grayish-black deposit was thick and adherent. The stomach contents were black in color, as were the feces of the small and large bowel.

Microscopically, the esophageal mucosa at the edges of the perforation was normal stratified squamous epithelium. In the submucosa and the muscularis, the blood

FIG. 1. Mucosal view of esophagus and stomach. The rupture is just above the cardio-esophageal junction.

vessels were distended and congested. Cellular infiltration consisting of neutrophils, lymphocytes and macrophages was present in a dense network of fibrin deposit and debris in the adventitia and periesophageal tissues.

Case 2. A 43 year old white female was well until the morning of admission, when she awoke with colicky epigastric and substernal pain accompanied by vomiting and retching. The vomitus was described as consisting of undigested, foul-smelling food particles and coffee-ground material. A local physician was called who gave an unknown amount of morphine. Relief was slight and, following this medication, the patient again began to vomit. She admitted to a heavy alcoholic intake for many years, and had been drinking a good deal during the night previous to admission.

When first seen by a physician on the staff of St. Vincent's Hospital, she was

moaning and showing great agitation. The skin was cold and moist, and the blood pressure was 100 mm. Hg systolic and 60 mm. diastolic. Heart and lungs were negative except for a few fine moist râles in the interscapular region; and no subcutaneous emphysema was present. On admission, the diagnoses of bleeding peptic ulcer, acute gastritis and esophageal varices, as well as ruptured esophagus, were entertained.

A chest roentgenogram taken on admission was read as showing accentuated markings, and there was an area of infiltration and exudation in the left base believed to be due to pneumonia. No mediastinal emphysema was observed. Other laboratory data included a red cell count of 4.5 million and a white count of 16,700 with 88 per cent neutrophils. Two other white counts done during the illness were 24,000 and 20,000 with 93 per cent and 88 per cent neutrophils, respectively. The blood sugar, total serum protein and urea nitrogen values were normal. An electrocardiogram showed only a sinus tachycardia at a rate of 120. One blood culture was reported as negative, and one benzidine test on the stool was negative for blood.

By the afternoon of the first hospital day the abdomen was soft and nontender but there was pain associated with respiration. On the morning of the second hospital day the temperature had risen to 102° F. and a loud pleural rub was audible at the left base in the axillary line. Fine, sticky râles could be heard in the area, and the percussion note was dull. The diagnosis of acute fibrinous pleurisy was made, and beginning aspiration pneumonia of the left lower lobe was considered. Esophageal varices and peptic ulcer were still entertained as etiologic agents for the hematemesis. Penicillin therapy was begun at this time.

The temperature remained elevated and by the third hospital day there were evidences of fluid in the left chest and dullness and bronchial breathing at the right base. Oxygen was required because of dyspnea. Complaints of left anterior and left lateral chest pain were constant and only slightly relieved by medication. A chest roentgenogram at this time revealed the entire left lung to be obscured by pleural fluid, and multiple small fluid levels were apparent. The right base was obscured by a small amount of pleural fluid. Because of the extremely rapid progression, an esophageal rupture was then considered to be the most likely diagnosis.

On the fifth hospital day the temperature dropped to normal but rose again quite rapidly. A thoracentesis performed on this day yielded 300 c.c. of thin bloody fluid, the last 50 c.c. of which had a definite fecal odor. Streptomycin was begun at this time.

Despite antibiotics, intravenous fluids and oxygen, the patient became stuporous, respirations were labored and rapid, and numerous râles were heard at both bases. Death occurred during the early morning of the sixth hospital day.

Necropsy revealed the abdomen to be essentially negative. There was no evidence of hemorrhage or peritonitis. When the thorax was opened, the pericardium was seen to be covered by a fibrinopurulent exudate. A similar purulent exudate blanketed the pleural surfaces of both collapsed lungs. In each pleural cavity there was a collection of turbid yellow fluid, approximately 700 c.c. on the left and 600 c.c. on the right. An inflammatory exudate in the posterior mediastinum obscured the outlines of aorta and esophagus and bound them firmly together. Grossly and microscopically, both lungs were atelectatic and congested, and contained areas of bronchopneumonia. A well circumscribed abscess was found in the interlobar septum of the left lung.

When the esophagus was opened, an oval-shaped longitudinal perforation, measuring 2.5 cm. in its long axis, was found in the posterior wall immediately proximal to the cardio-esophageal junction (figure 2). The edges of the perforation were sharply delimited and the mucosa was gray and intact, except for a blackened linear mucosal hemorrhage 4 cm. in length and 4 mm. in width, located above the perfora-

tion. Bloody mucoid material was found in the stomach, and the feces in the terminal ileum and colon were black.

Microscopic examination of the esophagus revealed an intense inflammatory cellular infiltration in the esophageal mucosa and submucosa, and in the periesophageal and mediastinal tissues. Fibrin composed the bulk of the inflammatory mass, although granulation tissue could be identified.

FIG. 2. Periesophageal inflammatory tissue can be seen through the rupture located immediately above the cardia. A transverse portion of diaphragm remains attached at this level. Above the rent is a linear mucosal hemorrhage.

DISCUSSION

Significant in the history of both patients, who were in the younger age group, is the presence of heavy drinking, vomiting of fluid containing blood, and severe epigastric and substernal pain unrelieved or only partially relieved by morphine. These findings have been emphasized by most reviewers and are of importance not only from the standpoint of diagnosis but also of pathogenesis.

The vomiting reflex, being a complex one, is evidently disturbed by persistent retching alone, or in conjunction with alcoholism, so that in the process of vomiting the sphincter at the cricoid level fails to relax. Theoretically, this failure would then result in a transference of pressure generated by the abdominal musculature and diaphragm to the esophagus. Experiments in the cadaver indicate that pressures in the neighborhood of 3.5 lbs./sq. in. are capable of causing esophageal rupture, and although the actual vomiting pressure has not been measured it is assumed to be well above this figure.[10] It is of interest that rents produced in this artificial manner are longitudinal in direction and are located

in the lower segment, usually just above the diaphragm. Etiologies other than vomiting which may increase the intraesophageal pressure, such as defecation, epilepsy and indirect trauma, have been recorded.[1, 11] Nevertheless, cases have also been reported in which no cause for increased pressure is evident, and the lack of such a history can not exclude rupture in any instance in which physical findings and laboratory data are confirmatory.[1, 9]

Unfortunately, neither of our cases on admission presented the valuable diagnostic sign of subcutaneous emphysema about the upper chest and neck, which is present in from 50 to 60 per cent of the reported cases.[1, 10, 6] In each instance, however, there were peripheral circulatory collapse and abdominal rigidity, which led in the first case to the most common diagnostic error, that of perforated peptic ulcer. Abdominal rigidity is an intrinsic part of the clinical picture in these cases and is probably due to the mechanisms for respiratory splinting rather than peritoneal irritation, particularly in the absence of tenderness. The presence of chest signs early in the course of the disease is also of important diagnostic significance, for if in an acute illness evidence is obtained of fluid or air in the pleural cavity or mediastinum, and the gastrointestinal tract can be incriminated on the basis of grossly bloody vomitus, the diagnosis of a ruptured esophagus is indicated. Perforation of a diaphragmatic hernia may, of course, mimic these findings.[13]

In addition to the salient features of the history, physical examination and standard abdominal and chest films in the upright position, certain laboratory aids have been described which permit confirmation of a suspected rupture and allow surgery to be undertaken without perturbation. If pleural fluid is detected, it may be aspirated and tested for hydrochloric acid content. This procedure in one instance yielded fluid containing 55 degrees of total acidity.[9] Grossly, aspirated fluid has been described variously as turbid and straw colored, brownish, often resembling vomitus, and possessing a foul odor or the odor of recently ingested food. A second test utilizes a radio-opaque substance which is administered orally, and its appearance in the pleural cavity is detected by fluoroscopy or roentgen-ray.[7, 9, 13] Although the use of these contrast media is considered academic by some, who rely on the presence of air or fluid in the standard chest films,[4] the original roentgenograms in our second case did not offer confirmation of a rupture, whereas the use of a radio-opaque substance at that time might well have been conclusive.

Probably the most striking similarity in the cases described in the literature and in the two cases we observed is the appearance and location of the rupture. It is longitudinal in direction, with sharp, well-defined borders, and is surrounded by normal mucosa. A predilection exists for the posterior wall, and it is found so much more frequently on the left than on the right that a left surgical approach has been advised if doubt exists.[14] In a review of 53 cases, Barrett was able to find only two instances in which the perforation was not limited to the lower end. The gross and microscopic evidence of acute inflammation in the esophageal wall and mediastinal tissues is of importance in excluding the possibility of postmortem perforation, a rather common finding. In order to eliminate other sources of confusion, such as might arise from opening the esophagus through the rent, or possibly, from having incised the esophagus at the time of necropsy, we have found it useful to introduce water slowly in the upper end

above the arch of the aorta before any manipulation, and to observe its exit through the rent. This also affords a better in situ evaluation of the location of the lesion.

From a consideration of the size of the esophageal opening, the degree of mediastinal and pleural contamination, and the respiratory embarrassment caused by excessive amounts of fluid and gas in one or both pleural cavities, it is not difficult to understand the necessity for surgical measures to insure proper drainage. Such has been the treatment in the five reported cases of survival.[2, 5, 8, 13, 14] Feasibility of prompt transpleural surgical repair of a spontaneous esophageal rupture was first demonstrated by Barrett,[2] although the most promising results, in ultimate function and duration of convalescence, were obtained by Olsen and Clagett, who utilized a transpleural approach with drainage of both mediastinum and pleural cavity, modern supportive therapy and the antibiotics. The inadvisability of delaying prospective surgery in the hope of decreasing the operative risk is amply demonstrated by the high mortality, by our experience and by that of others.[10]

It is to be confidently anticipated that the frequency of early diagnosis will increase proportionally with the awareness of this clinical and pathologic entity. With an early diagnosis, the opportunity for surgical intervention is presented and recovery rendered possible.

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UNUSUAL TOXIC REACTION TO BROMSULFALEIN *

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BECAUSE of the unusual toxic response that a patient exhibited to the intravenous injection of bromsulfalein (phenoltetrabromphthalein sodium sulfonate), and because of the scarcity of reports in the medical literature concerning reactions from this dye, this case report is submitted.

CASE REPORT

A 50 year old white woman was admitted to the hospital with the chief complaint of anorexia, easy fatigability, generalized weakness and abdominal pain of six weeks' duration. During the three weeks preceding admission this condition had become progressively worse, so that the patient was unable to perform her household duties and had to spend most of her time in bed. Six weeks before entrance the patient was awakened one morning by a severe attack of pain in the right upper and lower abdominal quadrants, radiating into the epigastrium and to the back. The abdominal pain gradually diminished in intensity, but persisted until admission to the hospital. The patient avoided all food with the exception of cereals and tea, believing that the pain was aggravated by the ingestion of food. Fever had been present for three weeks, ranging between 101 and 103° F. The fever was not accompanied by chills or chilly sensations. Frequency of urination and nocturia had been present for a week prior to admission. The patient also complained of a 30 pound weight loss over a period of one month. The past medical history revealed an attack of severe pyelitis following a hysterectomy in 1945. Careful questioning of the patient failed to elicit any evidence of hay fever, bronchial asthma, contact dermatitis, drug sensitivity or allergic reaction of any kind.

Physical Examination: The patient was an obese 50 year old white woman, lying comfortably in bed. The temperature was 98.6° F., the pulse rate 80 beats per minute, and the blood pressure 110 mm. Hg systolic and 64 mm. diastolic. Examination of the lung fields was negative. Auscultation of the heart revealed a soft, pulmonic systolic murmur. Examination of the abdomen revealed a large, irregular, tender mass originating in the right upper quadrant and extending into the pelvis. The obesity of the patient made it impossible to determine with certainty the nature of this mass, but it was thought to be either kidney or liver. The spleen and left kidney were not palpable. The remainder of the physical examination was negative.

Laboratory Data: The hemoglobin was 12 gm., the erythrocyte count 4,270,000 per cu. mm., and the leukocyte count 9,950, with a normal differential count. Urinalysis showed a 4 plus albuminuria and a large number of leukocytes per low power field. The Wassermann and Kahn tests gave negative reactions, serum bilirubin was 0.9 mg. per cent, urine urobilinogen was positive in dilution of 1:40, and blood urea nitrogen was 12.2 mg. per cent. A roentgenogram of the chest and a cholecystogram were within normal limits. An intravenous urogram revealed a large hydronephrotic right kidney with numerous calculi in the region of the lower pole, and several smaller calculi in the region of the pelvis and the upper pole. An electrocardiogram made on February 7, 1948, revealed a tendency to mild left axis deviation.

It was the impression of a physician that this patient had hydronephrosis of the

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right kidney, complicated by a mild attack of infectious hepatitis without clinical jaundice. To substantiate this impression various liver function studies, including a bromsulfalein test, were performed.

On the morning of February 8, 1948, at 8:55 a.m., the patient received 3.5 c.c. of bromsulfalein dye intravenously. This represented a total dosage of 175 mg., at 2 mg. per kilogram of body weight. Approximately three minutes after injection of the drug the patient became severely dyspneic, cyanotic and apprehensive. Examination at this time revealed the pulse rate to be 116 per minute, the respiratory

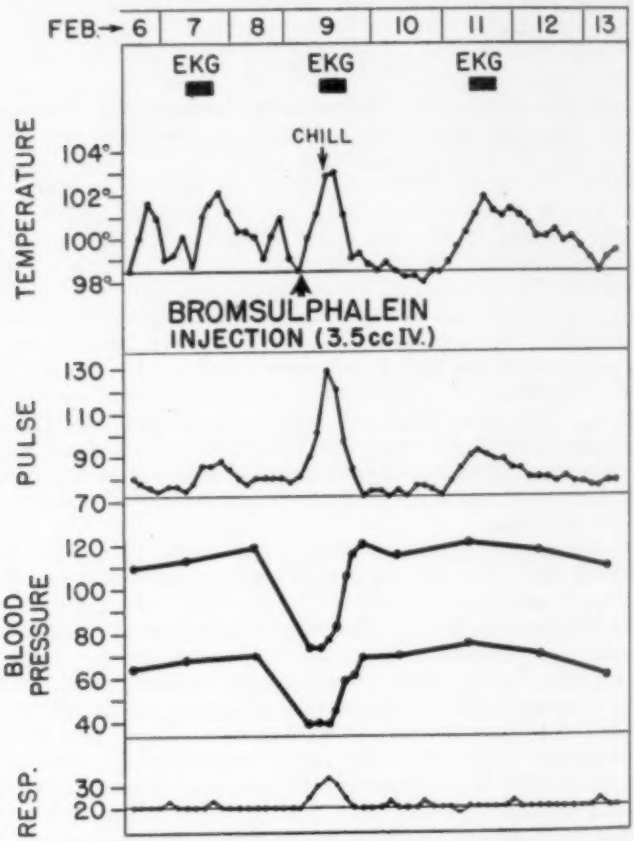

FIG. 1. Immediate systemic response to bromsulfalein injection.

rate 30 per minute and the blood pressure 70 mm. Hg systolic and 40 mm. diastolic. On auscultation of the chest, inspiratory musical wheezes were heard throughout the lung fields, as were occasional moist basal râles. The patient then began to complain of precordial pain and tightness. She was immediately given oxygen with a mask. Twenty minutes after the injection, the blood pressure was found to be 70 mm. Hg systolic over 36 mm. diastolic. She responded well to the administration of oxygen, as evidenced by the disappearance of cyanosis. In about 30 minutes the blood pressure slowly started to return to normal. At this time the patient suddenly experienced a severe shaking chill. The temperature at the peak of the chill was 103° F. and the

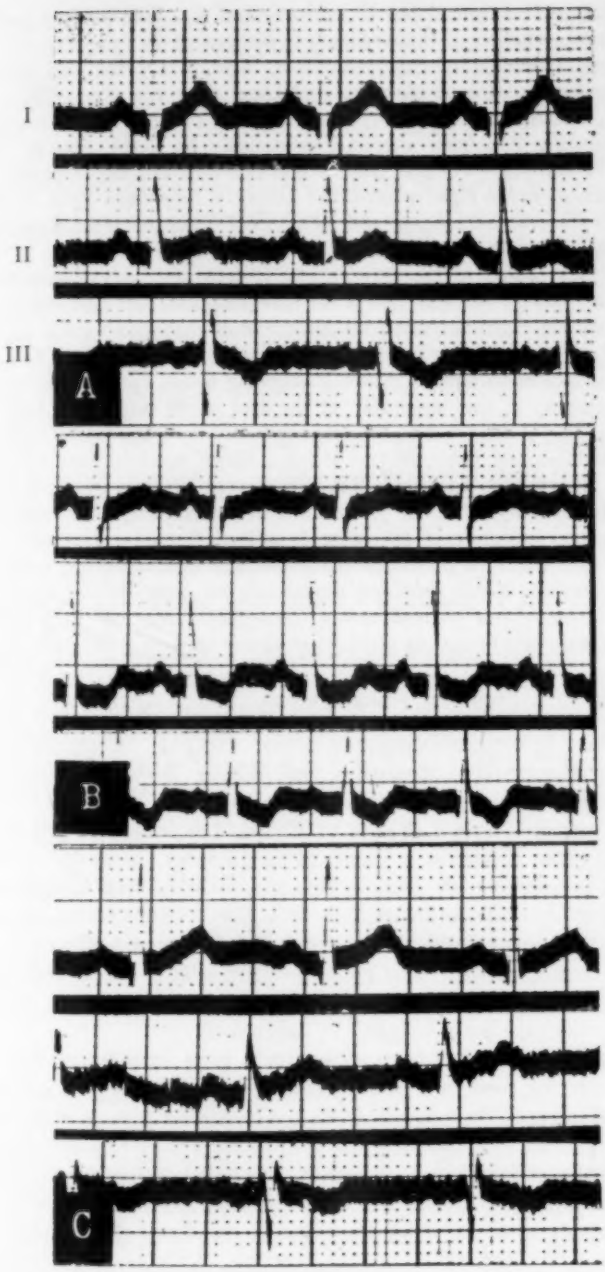

FIG. 2.

A. Electrocardiogram taken day after admission to the hospital, February 7, 1948.
B. Electrocardiogram taken four hours after reaction to bromsulfalein injection on February 9, 1948, indicating early right ventricular strain.
C. Electrocardiogram taken on February 11, 1948, revealing return of electrocardiographic pattern to original status.

pulse rate was 130. The chill lasted 15 minutes and was followed by profuse sweating. Graphic representation of this reaction is illustrated by figure 1.

An electrocardiographic tracing was made later that same day because of the patient's persistent complaint of pain and tightness over the precordial area. Compared with the tracing done two days earlier, the change was remarkable. The contour of the tracing had been altered considerably by depression of the ST segments in Leads II and III. As this patient had not received digitalis, this was interpreted as evidence of early right ventricular strain. Two days later (February 11) another electrocardiographic tracing was obtained. This electrocardiogram revealed return of the pattern to its original status, indicating the reversibility of the change.

On the patient's return to the Out-Patient Department several months after discharge from the hospital, a sensitivity test for bromsulfalein was performed. Using the ventral surface of the right forearm, an intradermal injection of 0.1 c.c. of a 1:10 dilution of the dye (representing 0.5 mg.) was given. At the end of 24 hours a fiery red macular area, tender to palpation and measuring 6 cm. by 7 cm. in diameter, was noted. This area was of the same size at the end of 48 hours but had changed in color to a dusky red. This reaction was accompanied by complaints from the patient of generalized malaise and pains in the joints. Since bromsulfalein has been found toxic to tissues, five young, healthy adult males were used as controls to determine what part this factor played in the production of the skin reaction observed in our patient. Intradermal injection of the same dosage of the same dilution of the dye in the forearms of the controls produced instantaneous erythematous areas measuring 2 to 3 cm. in diameter, which subsided completely or were barely visible within 24 hours. The response of our patient to the intradermal injection of a dilute solution of bromsulfalein was interpreted as positive evidence of sensitivity to the drug.

Discussion

Bromsulfalein (phenoltetrabromphthalein sodium sulfonate) came into clinical use after the work of Rosenthal and White [1] in 1925. They found that substance to be ideal as an index of liver function. In studying the toxicity of this dye they [2] reported that a dosage of 50 mg. per kilogram proved fatal in a dog four hours after injection. Their usual findings, however, were that no symptoms were produced with doses of less than 100 mg. per kilogram except an occasional transitory chill following the injection. Above this amount, death occurred in 50 per cent of the animals, either at once or within 12 hours with chills and weakness. Gruber [3] has noted definite falls in blood pressure in laboratory animals who have received the recommended USP dose of bromsulfalein (2 mg. per kilogram body weight) intravenously.

The bromsulfalein test has been extensively used throughout the world but, amazingly enough, the first case of a severe toxic reaction in the human was observed by Chambers and Moister [4] in 1946. The toxic response observed by them was in the nature of an acute allergic reaction occurring in a patient with a history of bronchial asthma of four years' duration who exhibited severe sensitivity reactions to many substances. This reaction occurred immediately after the intravenous administration of the drug in a dosage of 5 mg. per kilogram of body weight, and was characterized by severe dyspnea, cyanosis, loss of consciousness and clonic convulsions. Other observers have reported mild reactions after administration of the drug intravenously. Elevations in temperature, nausea and vomiting, transient headaches and mild allergic phenomena associated with urticaria and asthma have been observed clinically.

The reaction observed in our patient presents several interesting features. The probability of an immediate allergic reaction due to hypersensitivity to the drug is strongly suggested by the promptness with which the patient's symptoms appeared. The respiratory response, as evidenced by dyspnea and cyanosis, was accompanied by peripheral-vascular collapse, shown by the fall in blood pressure and the acceleration of the pulse rate. It is of interest to note that the amount of pulmonary involvement was severe enough in its effect on cardiac function to give rise to electrocardiographic findings indicative of early right ventricular strain. Whether the pyrogenic component which was observed forms a part of the allergic response is uncertain. Such a reaction could easily have been attributed to impurities rather than to the dye itself.

We agree with Chambers and Moister in that caution should be used in the injection of the dye, especially if the patient furnishes a history of bronchial asthma, hay fever, contact dermatitis, or other allergic reactions of any kind. One centimeter (50 mg.) should be injected slowly and an interval of several minutes allowed, to note any unusual response. The remainder of the drug should then be injected slowly. These precautions should be followed particularly if the higher dosage (5 mg. per kilogram of body weight) is used.

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DERMATOMYOSITIS AS AN INDEX OF MALIGNANT NEOPLASM: REPORT OF A CASE AND REVIEW OF THE LITERATURE*

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Dermatomyositis is a fairly well-defined clinical entity, usually readily distinguishable from lupus erythematosus disseminata, scleredema, early scleroderma, pellagra and trichinosis, the conditions it most closely resembles. Little is known of the possible causative factors, the general belief being that the disease perhaps has some toxic or infectious basis. Streptococci have been particularly suspect because of the frequently obtained history of sore throat, scarlatina or other acute respiratory infection preceding the appearance of dermatomyositis.[1, 2, 3, 4, 5, 6] Some investigators have been able to isolate streptococci, staphylococci

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and other organisms [7] from the affected muscles, and Ormsby and Montgomery [8] state that "autogenous vaccines, when cultures of muscle are positive, are definitely valuable," indicating that the organisms thus obtained are of etiologic importance. Tuberculosis has been thought to be a causative factor in three cases,[9, 10, 11] while in two cases reported by Dostrovsky and Sagher [12] dermatomyositis was associated with malignant visceral new growths. This combination was also noted in the authors' case, and in a review of available literature 17 such instances were found. Sites of the neoplasms were as follows: ovary, four [12, 13, 14]; stomach, three [15, 16, 17]; breast, three [12, 14, 18]; reticuloendothelial system, three [18, 19, 20]; esophagus, one [16]; gall bladder, one [5]; vagina, one [21]; rectum, one.[7]

Case Report

A 47 year old woman was admitted to the Department of Dermatology, University of Illinois Research and Educational Hospitals, on January 26, 1948. Except for a partial hysterectomy for uterine fibroids in 1942, she had been well until three months previously, when a red, pruritic eruption appeared on the V of the neck and spread rapidly to the arms and face. Two weeks after onset of the eruption the leg muscles became painful, tender and increasingly weak, and by the time the patient entered the hospital she had to be assisted to sit up, and was able to walk only a few steps because of generalized muscle weakness. She was afebrile during the period

Fig. 1.

of observation, although low-grade fever had been present at the onset of illness. Examination revealed marked periorbital edema (figure 1) and telangiectasia of the lids, producing the heliotrope discoloration characteristic of dermatomyositis. A patchy, erythematosquamous, telangiectatic and pigmented eruption covered almost the entire body, affecting particularly the face and neck and the extensor surfaces of the forearms and thighs. Quarter-sized superficial necrotic crusted areas were noted on the dorsa of the hands and the sides of the neck and face. The limb muscles were tender and of a peculiar boggy consistency. Examination in the Department of Physical Medicine revealed moderate loss of power of affected muscle groups. The remainder of the general physical examination was negative. Laboratory findings were as follows: erythrocytes 4,060,000, leukocytes 9,350, with a differential count of 73 per cent polymorphonuclears, 7 monocytes, 19 lymphocytes and 1 eosinophil; sedimentation rate (corr.) 32 mm. per minute; urinalysis negative for sugar, albumin or cells; urea clearance 58 per cent; blood non-protein-nitrogen and urea 33 and 13.5 mg. per 100 c.c., respectively, and A/G ratio 3.6/2.4. The lung fields were clear on roentgen-ray examination, and barium study of the upper and lower gastrointestinal tract was negative. Biopsy of the deltoid muscle showed a round cell infiltrate about the interseptal blood vessels and minimal increase in interseptal connective tissue. There was moderate hyperkeratosis and follicular plugging of the overlying skin, and the epidermis was thinned and atrophic. Several large areas of edematous fluid accumulation were present in the corium, along with a mild perivascular lymphocytic infiltrate. The findings were interpreted by Dr. Granville A. Bennett * as consistent with the diagnosis of dermatomyositis.

During her hospital stay the patient continued to complain of weakness, difficulty in swallowing, and pain and tenderness in the affected muscles. Courses of parenteral penicillin (total dose 8 million) and streptomycin (20 gm.) produced no change in the clinical picture. She was discharged, unimproved, with the recommendation that she continue with injections of foreign protein (Proteolac), and a high protein diet supplemented with amino-acids (Amigen).

On November 1, 1948, approximately 12 months after onset of the condition, she returned to the clinic because of abdominal swelling, first noted two months previously. Cutaneous and muscular manifestations were essentially as on previous examinations. There was a mass in the right lower quadrant of the abdomen, hard, firmly fixed, and extending superiorly to the level of the umbilicus. Vaginal examination confirmed the fact that the tumor arose from the pelvis, and the patient was transferred to another hospital for exploratory laparotomy. At operation the right ovary was found to be replaced by a large cystic mass which filled the posterior cul-de-sac and extended upward to the level of the umbilicus. Laterally, the tumor infiltrated the wall of the cecum and was fixed to the pelvic peritoneum. The neoplasm was considered inoperable, and the abdomen was closed after removal of a specimen for biopsy study. The pathologist's report was as follows: "The tumor mass is composed of anaplastic, pleomorphic hyperchromatic cells with distinct nucleoli. In some places the cytoplasm is clear, and in others, eosinophilic. The tumor has invaded the stroma. No definite structure can be made out at present, even though it appears to be ovarian tissue. Diagnosis: Compatible with very anaplastic carcinoma of the ovary, probably granulosa cell type."† Roentgen-ray therapy was started in the immediate postoperative period, and a total of 5,940 r at 250 PKV was given by cross-fire from four ports. During the course of treatment a freely movable, nontender, marble-sized nodule developed in the right breast, and was found on microscopic examination to be a metastasis from the ovarian neoplasm. A second course of roentgen-ray treatments, totaling 2,124 r, was given six weeks after the initial treatment.

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Unexpectedly, the cutaneous lesions began to fade soon after completion of the first course of roentgen therapy (figure 2) and muscle power increased perceptibly. The areas of superficial cutaneous necrosis, which had been recurrent during the entire course of the illness, now healed, and no new lesions appeared. Improvement was maintained during a three-month postoperative observation period.

FIG. 2.

DISCUSSION

It would be difficult to assign a causative rôle to the malignant neoplasm present in this and other reported cases of dermatomyositis on a statistical basis alone. The actual percentage of all cases of dermatomyositis in which malignant lesions develop cannot be calculated, and it might be argued that the association of the two conditions in the 18 reported instances is purely fortuitous. However, in our case, and in two others [12, 14] in which the tumor was treated, unequivocal improvement in the manifestations of dermatomyositis quickly followed, an occurrence which adds much weight to the inadequate statistical data. It must also be admitted that the mechanism by which neoplasms operate in the causation of dermatomyositis is obscure. Perhaps, as has been suggested for the cases following infection or intoxication, the disease depends on some as yet unclassified type of allergic sensitization. The necessary antigenic stimulus may be provided by products of tumor growth or breakdown as well as by bacterial or other proteins. Ancillary evidence of the allergic nature of dermatomyositis may be found in the frequency of eosinophilia [22, 23, 24] and in

the development of urticaria, erythema multiforme and erythema nodosum in early stages of the disease.[4, 23] Whatever the connection between the malignant neoplasm and dermatomyositis may eventually prove to be, their association is apparently frequent enough to justify thorough investigation in all cases of dermatomyositis to rule out underlying cancer, as is routinely done in acanthosis nigricans.

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CODEINE POISONING: FATAL CASE FROM ACCIDENTAL OVERDOSE*

By V. H. Cornell, M.D., F.A.C.P.,† *Washington, D. C.*

Codeine and its salts are so universally used, and poisoning due to these drugs is so rare, that the publication of this case appears warranted. Various authors have been consulted,[1, 2, 3, 4, 5, 6, 7] and fatal cases are reported as "rare," "not found" or "unknown," though severe symptoms and collapse have occurred after large doses. Cases have recovered after taking approximately 500 to 520 mg., but in such cases immediate therapy or vomiting may have greatly reduced the dose absorbed. Nausea and vomiting are given as frequent and prominent symptoms in codeine poisoning.[4] Gonzales, Vance and Helperin [3] give the lethal dose as 4.5 to 8 gr. but refer to recovery from larger doses.

The limit of therapeutic dosage is placed at 133 mg. (2 gr.),[1] and 4 gr. are reported to have given serious symptoms.[5]

Krueger, Eddy and Sumwalt [7] refer to the statement of Lochboehler, made in 1899 (J.A.M.A. **33**: 1397, 1899), that no case of fatal poisoning with codeine had been recorded, and state further that they found no record of any. This was in 1943. A recent search of the Index Medicus discovers no case reported in the past 10 years. However, the same authors refer to death in a case of acute asthma after use of codeine, reported by Cohen and Rudolph in 1932.[8] The original article does not state the dose consumed.

Edmunds and Gunn [4] warn that the use of codeine in cases where there is abundant or excessive secretion is "unnecessary and may be harmful." Cohen and Rudolph [8] condemn the use of opiates in asthma and, in addition to the depressant respiratory action and the abolition of the cough reflex, suggest a possible bronchial allergic reaction adding to that already present. They refer to a wheal production in all persons on intracutaneous injection of opiates, and the itching in many patients under opiate medication. In view of the extensive and, at times, indiscriminate use of "codeine cough mixture," these statements should be more carefully evaluated and considered in practical therapeutics.

Goodman and Gilman [6] report codeine one-fourth as depressant to respiration as morphine, and consider that the lethal dose cannot be stated. They contrast the fate of morphine and codeine in the body, 90 per cent of the former being destroyed, whereas 80 per cent of codeine is excreted in the urine. This is of interest in view of our toxicologic findings in the present case.

Case Report

The patient was a 30 year old white male known to be an habitual heavy drinker with a history of asthmatic symptoms for 20 years. There had been no real seasonal distribution, and attacks had become less frequent, less severe and shorter in duration, but he had entered a hospital at least once for therapy in 1943. Allergy tests showed 3 plus reactions to dust, horse serum, timothy and ragweed antigens, and 1 plus to horse epithelium, silk, wool and pyrethrum; numerous other antigens gave negative readings.

* Received for publication May 30, 1949.

† Colonel, Medical Corps, U. S. Army; Chief of Laboratory Service, Walter Reed General Hospital, Washington, D. C.

His current attack had lasted about seven days when he was admitted to the hospital in September, 1947. His past history was otherwise irrelevant except for pneumonia at age 10, and a record of appendectomy, tonsillectomy and adenoidectomy at unstated age. He showed "typical asthmatic breathing" and a "typical expiratory wheeze," with some inspiratory wheeze. There was slight dyspnea, and a few sibilant râles were heard in both bases.

Chest roentgenogram was reported negative; erythrocytes were 5,010,000; hemoglobin 101 per cent; leukocytes 9,550. Urinalysis was negative, with specific gravity of 1.023. The following medication was ordered: saturated solution of potassium iodide, 10 drops four times daily; adrenalin in oil, "0.5 c.c. every three hours p.r.n.," and adrenalin "1:1,000 sol. 0.5 c.c. p.r.n."; phenobarbital, gr. ½ four times daily; seconal, gr. 1.5 was given once daily for the first four days; brewer's yeast was given thrice daily after meals; penicillin was administered, beginning the fourth hospital day, 1,000,000 units every three hours. Brown's mixture was ordered the day before death but not supplied to the patient.

On the day preceding his death, the eleventh day in hospital, he and another patient consumed about a pint of whiskey between them before 9 a.m. He received the usual phenobarbital and brewer's yeast at 9 a.m. and at 1 p.m. He was seen in a nearby grill drinking during the afternoon and later sat on the porch with other patients, at which time he appeared drowsy and fell asleep several times. At about 3:15 p.m. he was seen to take two "swigs" from a cough mixture bottle on a neighboring bedside table. He appeared unusually sleepy during the early evening when he had a visitor, and at 8:30 was noted to be sleeping. The 9 p.m. medication was not given because he was asleep. At 1:10 a.m. he was asleep, and at 3 a.m. his snoring was heard by another patient. At 5:50 a.m. an attendant called the nurse and doctor: the patient had died.

Autopsy was performed four and a half hours after death. The principal findings were moderate pulmonary congestion, with much thick tenacious mucus throughout the right bronchial tree but little in the left lung; microscopic sections confirmed the congestion and excess secretion, some of which was purulent. Peribronchial hyperemia and infiltration by polymorphonuclears, round and plasma cells were marked, but eosinophils were not conspicuous. There were rather broad subepicardial hemorrhages between the vena caval orifices, which microscopically were seen to extend diffusely through the musculature of the right auricle. There was also some hemorrhage in the perivascular tissues about the left coronary, approximately 5 mm. beyond its origin. Other organs and tissues showed no significant changes.

TABLE I

Material	Ethyl Alcohol	Phenobarbital mg./100 gm. or c.c.	Codeine mg./100 gm. or c.c.
Stomach contents	0.12%	Absent	50.0
Brain	0.04%	0.4	0.5
Liver	0.04%	2.1	0.9
Urine	0.17%	1.6	12.5
Blood	0.04%	0.7	1.0

Toxicologic analyses * resulted in the findings shown in table 1.

The ammonia-ether soluble, ammonia-chloroform soluble, metallic, mineral acids and bases, halogens, oxyacids and special poisons were all absent. The materials were not analyzed for gaseous poisons.

* Toxicologic studies by Mr. Leo R. Goldbaum, Chief, Toxicology Section, Army Medical Department Research and Graduate School.

Table 2 summarizes the computations made from the above findings, and the recorded and estimated weights of organs.

Investigation revealed that the cough mixture which the patient had taken from his neighbor's bedside table was erroneously compounded to contain 7 *grams* of codeine sulfate, instead of 700 *milligrams,* in the 240 c.c. ordered. This is equivalent to 875 mg., or about 13 gr. per ounce. From evidence obtained, about 1 to 2 oz. of the medicine was consumed by the deceased. This would be equivalent to between 875 mg. (13 gr.) and 1,750 mg. (26 gr.) of codeine sulfate.

TABLE II

Material	Wght. or Vol. (gm. or c.c.)	Codeine mg. per 100 gm. or c.c.	Total Content mg.
Brain	1,180	0.5	5.9
Liver	1,825	0.9	16.4
Stomach	1,000	50.0	500.0
Urine	205	12.5	25.6
Blood*	6,176	1.0	61.8
	(Total from materials analyzed)		609.7 mg.
Heart	305		
Lungs	1,069		
Spleen	142		
Kidneys	254		
Intestines	2,500 (est.)		
Pancreas	60 (est.)		
	4,330	1.0 (est.)	43.3
	Estimated total in organs		653.0

* Blood estimated as 8% of body weight; 170 lbs. equals 77.2 kg.; 8% of 77,200 gm. is 6,176 gm.

In table 2 we estimated the organ content at about 653 mg. (10 gr.), of which 500 mg. was in the gastric contents. Deducting this amount from the estimated total leaves 153 mg. in the rest of the organs. The organs totaled about one-fifth the estimated body weight. It is considered approximately safe to estimate the total body content at thrice that in the organs, namely, 459 mg. (7 gr.). Based on total body fluid, it may be computed at the blood level as approximately 496 mg. (7.5 gr.). (Eighty per cent of blood as water and 80 per cent of body weight as fluid gives 0.80 of 1.0 = 0.8 mg./100 c.c. and 80 per cent of 77.6 kg. equals 62 kg. 0.8 by 620 = 496 mg.)

By the same ratios as used for codeine, the organ content of phenobarbital is computed as 88.2 mg. (1⅓ gr.), and this tripled would give 264.6 mg. (4.0 gr.), which may well be true, as he had received about 2 gr. a day for 10 or 11 days, and had received at least 1 gr. in the 24 hours preceding death. This undoubtedly would contribute to the depressant effect of the codeine and perhaps would mask other symptoms. It may have prevented the vomiting which has apparently saved others in cases of overdosage. By the time of death, or at least by the time of toxicologic examination, the alcohol content was negligible.

The auricular hemorrhage in the region of the sinoauricular node may have been the immediate cause of death. This hemorrhage could have been due to the anoxia and resultant increased vascular permeability.[9]

Summary

A case of accidental codeine poisoning is presented in which, due to an error in a prescription, the patient consumed between 875 mg. (13 gr.) and 1750 mg. (26 gr.) of codeine sulfate. This is considerably above the previous doses from which recoveries have been reported. The only previously reported death due to codeine [8] also occurred in an asthmatic patient, but the dose consumed was not recorded.

Phenobarbital was present within therapeutic range but may have masked symptoms and contributed to the depression. The patient was a known alcoholic and had partaken fairly heavily of alcohol in his last 24 hours, but analyses indicated it had all been oxidized or excreted. The codeine blood level found at autopsy was 1 mg. per 100 gm. of blood.

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TORULA HISTOLYTICA MENINGO-ENCEPHALITIS: FURTHER REPORT *

By Mark Marshall, M.D., F.A.C.P., and R. Wallace Teed, M.D., *Ann Arbor, Michigan*

In 1942 we [1] reported the case of a white girl, aged nine years, who came to the hospital because of headache, fever, nausea, vomiting, deafness and a regressive personality change. She was found to have bilateral masked mastoiditis which, with an associated localized meningitis, was thought to explain the symptoms. The left mastoid was opened and found to be destroyed, with thick mucopurulent material inside. There was a dural exposure in the tegmen antri, with a dural granuloma. Spinal puncture released clear fluid under great pressure

* Received for publication June 2, 1949.

(more than 600 mm. water) containing large numbers of Torulae, which were later grown on culture also. About a week later the right mastoid was opened and similar conditions were found. No Torulae were found in the granulation tissue taken at operation, or on culture of the mastoid. It was concluded that the mastoiditis was coincidental and in no way connected with the meningoencephalitis. The child was placed on sulfadiazine therapy and later on potassium iodide. She made an uneventful recovery in about four months, with no evidence of any neurologic residuum. Swelling of the nerve-head and retinal hemorrhages had been associated with the intracranial hypertension, but these gradually underwent resolution.

During the past six years the patient has been seen on a number of occasions and no evidence of recurrence has been noted. For two years or more she complained of occasional headaches, usually lasting from a few hours to two days, but there was never any indication that increased intracranial pressure existed. On a number of these occasions she was seen by an ophthalmologist, Dr. A. S. Barr, and by a neurologist, Dr. H. W. Riggs, but no indication for lumbar puncture was found. She returned to school in the fall of 1942 and quickly regained her place in her class. She is now in high school, doing creditable work with excellent grades. Her development physically, mentally and psychologically has been normal. She has had no illnesses other than occasional colds, from which she recovered promptly.

The ears have remained dry and the hearing is normal. The retinal hemorrhages were absorbed, and no disturbance of vision has been observed. No glasses have been advised. There are no evidences of paralyses, tics or muscle spasms.

No Torulae were noted in the last few spinal punctures done in 1942, and no indication for puncture has occurred since then. It was considered possible that the headaches might have been on the basis of increased intracranial tension, but they always subsided within a day or so and left with no residuum. No recurrence of papilledema or retinal hemorrhage was noted. Headaches have been very rare in the past four years. It is probable that they were due to another cause.

In our review of the literature up to 1942 we could find no case of torulosis of the central nervous system which could be considered completely cured. The same may be said for the literature to 1947. Lewin and Roux [2] reported a case (case 2, adult male) treated with sulfapyridine and penicillin, the latter being administered both intrathecally and intramuscularly. Later the patient was given potassium iodide. Eleven months after the onset of symptoms he was alive and well, and although the spinal fluid showed 24 lymphocytes per cubic centimeter, no Torulae were seen. Tinney and Schmidt [3] reported the case of a 25 year old man (case 3) with pulmonary cavitation and chronic meningitis. He recovered clinically following tyrocidine intrathecally and sulfathiazole per os. Eight months later he was asymptomatic and went on a hunting trip. It would be of interest to know the present condition of this man. Voyles and Beck [4] reported improvement in a 44 year old man (case 4) who became ambulatory after seven months. However, Torulae were present in the spinal fluid and urine.

We were impressed by the apparent curative action of sulfadiazine in our patient. For a week after her second mastoidectomy she improved so much that the drug was stopped and the patient was discharged. However, in three days she

was back again with the symptoms as before. Sulfadiazine was resumed, with disappearance of the symptoms in 48 hours, and the drug was continued for another 42 days. Following this, potassium iodide was given for three months.

Others have not been so impressed with the value of the sulfonamides. Beck and Voyles,[5] using dogs, rabbits, guinea pigs and mice, found no benefit from the use of sulfadiazine and potassium iodide. Jones and Klinck,[6] using mice, found no beneficial effects with either sulfadiazine or penicillin. Lewin and Roux [2] found Torulae resistant to penicillin on plate culture, as did Hamilton and Tyler,[8] and Harford, Martin, Hageman and Wood.[9] Hamilton and Thompson,[10] on the other hand, found that penicillin caused a marked drop in the number of fungi in the spinal fluid, but did not entirely clear the fluid. They also found the Torulae sensitive to penicillin in vitro, as did Hobby, Meyer and Chaffee.[11] Most of the cases reported within the past four years have been given either penicillin, sulfonamides, or both, to no avail.

It therefore cannot be said with finality that any drug is of undoubted value in this disease. However, in a condition with a mortality approaching 100 per cent, one is justified in using any therapy which may be of benefit. Mezey and Fowler [7] thought 5 per cent alcohol and dextrose intravenously were helpful. Spinal drainage is certainly helpful in relieving headache, and is advised. It is probable, however, that in the last analysis it is the "vis medicatrix naturae" which determines the outcome.

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EDITORIAL

THE PENNSYLVANIA HOSPITAL

In May of this year, the oldest hospital in what is now the United States entered its third century. The date of origin of institutions of a similar kind and age is often more or less in doubt, but in the case of the Pennsylvania Hospital the records allow no such obscurity. The charter given by the Assembly of the Province of Pennsylvania—with some reluctance to be sure—still is on exhibition at the hospital—bearing the date of January 23, 1751, and the minutes of the Board of Managers—carefully prepared and carefully preserved from the beginning—provide easily available original sources for all the important events in the hospital's existence. It was on May 5, 1751, according to the entry in the minutes in the handwriting of the then Secretary—Benjamin Franklin—that the organization meeting of the Contributors was held. On the past May 2 to 4, the hospital celebrated its 200 years of continuous service to the sick and injured, during which time there have issued from it noteworthy contributions to medical education and research. More significantly, however, as John N. Hatfield, its Superintendent and Administrator for 26 years, has recently emphasized, its foundation signalized the beginning of the voluntary hospital system in this country. Particularly in these perplexing times of our nation's history, it is well to stress that this pillar of the American way of life, "emblematic of the freedom, the self-initiative and the faith found still to be inherent in us," not merely survives—a matter of lesser importance—but still preserves its progressive vitality.

This may not be the place to follow even very briefly the thread of the hospital's story, but it will be done, nevertheless—both as an attempt to inform the readers of this Journal about one of our pioneer hospitals and its celebration and also in order to bring out lessons from its past which may serve as valuable precedents in solving some of today's medical problems.

The need for a privately run hospital for "The relief of the sick poor and for the reception and cure of lunaticks," had for some time been in the thoughts of Dr. Thomas Bond, a prominent Philadelphia physician who was to serve the hospital assiduously for many years. Perhaps his most valuable service to it, however, was in enlisting the aid of Benjamin Franklin, who was the chief instrument in getting the hospital established. As may be read in his Autobiography, he employed efficient methods, which some of us may in the conceit of our ignorance regard as "modern." To aid in procuring subscriptions he "endeavoured to prepare the minds of the people by writing on the subject in the newspapers, which was my usual custom in such cases." The assistance sought from the Assembly meeting with considerable opposition, he formulated a plan about which he later wrote: "I do not remember any of my political manoeuvres, the success of which

gave me at the time more pleasure." The plan was to get the Assembly to enact a bill with the proviso that when the contributors had raised £2000, the interest of which was to be used for the care of the sick poor free of charge, the provincial treasurer was required to pay £2000 for the building and finishing of the hospital. The bill was passed, as it was thought impossible to raise such a sum by subscriptions, but these now poured in "since every man's donation would be doubled, thus the clause worked both ways." It may be unnecessary to point out that millionaires and foundations have rediscovered this device in our own times. Franklin was Secretary of the Board for two years and then its President for four. Having inaugurated a system of fines for absence from meetings, he was the heaviest loser on account of many unavoidable absences on public business.

After a few years in temporary quarters in a rented house on High Street (now Market), the present site consisting of a solid city block, was bought for £500. The first unit of the plan which was designed by Samuel Rhoads, one of the hospital managers, the east wing of the "old building" was opened in December 1756. The cornerstone bears Franklin's justly famous inscription, "In the year of Christ//1755// George the Second happily reigning//For he sought the happiness of his people//Philadelphia flourishing//for its inhabitants were publick spirited," etc. The words may still be read with ease, perhaps because the stone was lost to sight for many years and accidently revealed during the course of repairs. Not a few of those who have seen it, now carefully protected, will agree that among cornerstones it is unsurpassed.

Well started, the fledgling hospital was solidly supported especially by the Quakers, long the wealthiest and most important element in the growing city, a group that still lives up to its reputation of doing well whatever it undertakes. The constant need for physical expansion, a condition that has burdened so many American hospitals, is shown in the hospital's latest pamphlet listing its chronological development—whereas a period of 50 years passed before the west wing and centre of the original building were completed, a comparable period, the last 58 years, has required the addition of nine large structures (Out Patient Department, Nurses Home, Surgical Pavilions, Garrett Memorial, Ayer Laboratory, New Out-Patient Building, The Pennsylvania Institute, The Women's Building, The Benjamin Franklin Clinic for staff physicians' offices (1946).

One might expect that in these 200 years, noteworthy contributions to medical theory and practice would have emerged from the hospital and one is not disappointed. Of the 20 physicians and surgeons appointed to the staff in the 18th century for instance, all but four achieved more than a local reputation. Among this group were Thomas Bond (founder of ward teaching and of clinical lectures in the U. S.); Thomas Cadwalader (early study of lead colic and first description of osteogenesis imperfecta); John Morgan (founder of the first medical school in U. S.); William Shippen (inaugurator in 1762 of the first considerable anatomical lectures—60 in

number—in the U. S.); Benjamin Rush ("The American Sydenham" and the greatest historical figure in American medicine according to Welch); Philip Syng Physick ("The Father of American Surgery"—"a discoverer, a thinker, a worker, but not an author"). Of these two more shortly. Also Benjamin Smith Barton (a pioneer American writer on botany, materia medica and other branches of natural history).

One of the managers, Benjamin Franklin, though not a professional physician, must also be included in this list because of his life long interest in and his contributions to medicine. His invention of bifocal spectacles and the circumstances leading up to it are now a well known story; perhaps less well known is an indirect benefit that he noted from them, namely, that the more distinct view that they gave him of the features of an interlocutor enabled him to understand better what was being said—an observation only recently rediscovered. The contagious nature of the common cold and consequently the merits of fresh air and demerits of closed windows were reiterated in his letters through many years. His views on "Diet and its effect on health and disease" were far in advance of his time. He invented a flexible catheter, made accurate observations on gout in his own person, and wrote well on lead poisoning, inoculation for smallpox, seasickness, the advantages of nursing at the breast, the effects of electricity in lethal doses and therapeutically in nervous disease and so on.

Much has been written in recent years about the achievements of Benjamin Rush; here one need merely note his enlightened views of the nature and treatment of mental disease, that have led to his being called our first psychiatrist, his correlation of focal infection in the teeth with disease in distant parts, his independent description of Dengue one year after Bylon's, his advocacy of occupational therapy and opposition to alcoholism. Physick, besides being one of the most skilled operators and lithotomists of his day, introduced the use of the stomach tube in this country. He also invented a tonsillotome, introduced the use of absorbable ligatures, and the helpful seton in ununited fractures and devised an operation for closing an artificial anus, and a splint for a fractured femur that outlived Desault's into the 20th century. In spite of his aversion to authorship, his work usually got into medical literature, in large part through his nephew, Dorsey.

In the second half of the hospital's first century, one notes such distinguished names as John Conrad Otto, whose masterly elucidation of the mode of inheritance of hemophilia in 1803, was the greatest single achievement of American medicine up to that time; John K. Mitchell (the theoretical importance of whose "Cryptogamous Origin of the Malarious and Epidemic Fevers" is ranked by Garrison with Henle's "Miasms and Contagions"). Hugh Hodge and C. D. Meigs, of dubious fame in their ill chosen stand against Oliver Wendell Holmes on the etiology of puerperal fever, but leaders both in obstetrics in this country notwithstanding; and W. W. Gerhard, renowned for his differentiation of typhus from typhoid

fever while a resident at the Pennsylvania Hospital in 1834 and staff physician at the Philadelphia Hospital during the epidemic of 1836.

Similar noteworthy milestones of progress might be recorded during the Hospital's second century, such as Morton's first planned appendectomy, and, more recently, the pioneer work in experimental and institutional study of functional nervous disease. It is in no sense derogatory, however, to assert that in general, over most of the hospital's existence the staff has been chiefly distinguished for its mastery of the existing medical knowledge of the day and its conscientious application to the welfare of the patient and the instruction of the medical students and residents under their guidance. As was said of Adam Kuhn, many of them were not remarkable for the power of imagination; but in sound judgment they greatly excelled. The principle expressed in Alexander Pope's:

"Be not the first by whom the new is tried—
Nor yet the last to lay the old aside" (Essay on Criticism)

was doubtless an important factor, though of course not applicable to investigative work. Such attitudes continue to be so successfully applied that the hospital could always be recommended as one of the very best either for the sick patient or for the eager student hunting for the best place to take his internship. All this I have borne in mind in talking to students seeking advice during many years of medical teaching in Philadelphia.

In these days, when we are belatedly returning to an appreciation of the more or less intangible in medical treatment—"psychosomatic" may be a new word but its truths and its use in therapy are as old as medicine itself—a word or two on morale and *esprit de corps* may be pardoned. These two essentials should come more easily to long established institutions; but I know of no place where they are more conspicuous than in the hospital that has just celebrated its 200th anniversary. It takes but a short time in such an institution to appreciate the atmosphere of pride in one's daily work, be it humble or conspicuous, that is a very satisfactory substitute for the restless striving to get ahead, often of the other fellow and not necessarily in one's task. Do not mistake this for a slothful ease; the well adapted not only works to better purpose but actually harder, and the hectic drive of unbalanced ambition may even be the undoing of its unfortunate possessor. But, as we know only too well, it takes all kinds to make a world even today. Those whose lot falls in the more orderly spheres are the fortunate ones. May some of them have the inborn endowment to accomplish mightily, as did Franklin, Bond, Rush and their associates of 200 years ago!

E. B. KRUMBHAAR

REVIEWS

Serum Sickness. By C. Frh. Von Pirquet, M.D., and Bela Schick, M.D.; translated by Bela Schick, M.D. 130 pages; 23.5 × 15.5 cm. The Williams & Wilkins Company, Baltimore. 1951. Price, $3.50.

It is now quite a few years since I first read the original of this book in German and it has been an interesting and enlightening experience to reread it, this time in the new English translation by one of the original authors, Dr. Bela Schick.

The monograph on Die Serumkrankheit which appeared in 1905 is outstanding and has long taken its rightful place as one of the medical classics. It should be required reading for all those students of medicine who are training to acquire those habits of mind so necessary to their own success in independent clinical and experimental research if their work is to be enduring.

My enthusiasm for this work is based upon the fact that I believe it portrays the workings of the medical mind at its best. The first two chapters—there are only three—relate the clinical research and are noteworthy for their painstaking recording of data from clinical studies so masterfully planned that not only the data but also the deductions on the nature of serum disease stand unchallenged today nearly half a century later.

Almost as much may be said for the third chapter on experimental research although here new technics such as quantitative precipitin estimations and passive transfer of skin-sensitizing antibodies have enabled us to separate the different antibodies of precipitation from those of the immediate edema wheal reaction of the skin. But it is interesting that even this was surmised by our authors 45 years ago when they say "these findings indicate that antibodies of the vital reaction are not to be identified with the precipitin" (page 102)—a thought that was completely overshadowed by Zinsser's unitarian theory of antibody function now proved inaccurate.

We are all fortunate indeed to have now secured this careful English translation by one of the original authors—a job that no one else could possibly have done as well—and we owe a debt of gratitude to Bela Schick for taking the time from his busy hours to make this classic available to the English reading medical profession. He has done us a great service.

Robert A. Cooke, M.D.

The Urinary Function of the Kidney. By A. V. Wolf, Associate Professor of Physiology, Albany Medical College, Union University. 363 pages; 24 × 15.5 cm. Grune and Stratton, Inc., New York. 1950. Price, $7.50.

This is one of the best and most comprehensive monographs on the subject of renal physiology to appear in recent years. The approach is primarily and solely functional, and matters relating to renal pathology do not intrude into the discussion except when they clarify the normal activity. For instance, diabetes insipidus is somewhat lengthily considered because of the physiological implications of the disease, whereas the word *nephritis* is not even mentioned in the index.

The author holds no brief for any special theory of renal function and maintains an admirable objectivity and detachment throughout the book. Perhaps no function of the body has suffered more indiscriminate hypothesizing than has the formation of the urine. Galen clearly recognized as early as 180 A.D. the relationship between structure and function in the kidney. The product of the kidney has always been obtainable in quantity. Through the years a vast body of conjecture has developed, much of which has borne fruit, while the rest has merely prompted endless hours of fruitless investigation to prove a point. Wolf avoids all such conjecture and hews to

the line with admirable restraint, proceeding, in the best tradition of the American school, to get the facts first and leaving the interpretation until later.

As already indicated, this is primarily a book for physiologists. However, a clinician who wants to understand the basic mechanism which operates to form the urine will find his answer here. The writing is as clear and as simple as the subject permits and the arguments move along smoothly. The modern concepts of clearance, Tm, threshold, etc., are handled skillfully and, while the treatment is at times a bit mathematical, the mathematics are not so difficult as to defy analysis by any determined person, even though he is not accustomed to thinking in this field. The organization of the book is logical and proceeds from a consideration of the physicochemical factors affecting water balance and fluid transfer through a consideration of renal physiology and body water compartments, to matters related to hydration, diuresis, etc. The final chapter on the endocrine control of the kidney is an excellent one and serves as a peg on which to hang the summary. No real understanding of the kidney is possible without an understanding of the rôle played by the hormones from the posterior lobe, adrenal cortex, adrenal medulla and thyroid. In the discussion of the adrenal cortex there seems to be an undue emphasis upon desoxycorticosterone, which is not surprising since this cortical steroid has been available in quantity and at reasonable cost for some time. However, there is today a strong tendency to regard its action as pharmacological rather than physiological.

It would be quite impossible to mention everything covered in this book, but its broadness and scope are further indicated by the fact that matters such as Verney's osmoreceptor theory, the postural effect on urine formation and the influence of environmental factors (such as sleep, temperature and emotions) on urine flow are discussed. The inclusion of a section on the possibility of the secretion of potassium by the tubule shows the author's willingness to admit new ideas. Hard and fast definitions are avoided and the plasticity and lability of living processes are recognized. Such matters as the size of the fluid compartments are not rigidly defined since it is well recognized that the validity of such measurements depends on the yardstick used in determining them. The vagueness and inability sharply to delineate boundaries may well be a characteristic in all living things. In any event, the physiologist thinks so.

The book has an excellent bibliography of 1189 titles, about two-thirds of which appeared after 1930. It might have been helpful to include references to some of the older monographs and reviews so that the student could, if he wished, find his way back into the earlier literature without great difficulty. The index is a bit disappointing. Such an excellent book really deserves a better one.

DIETRICH C. SMITH

Basic Principles of Clinical Electrocardiography. By HANS H. HECHT, M.D. 88 pages; 14 × 22 cm. Charles C Thomas, Springfield, Illinois. 1950. Price, $2.00.

This is another slender addition to the American Lecture Series. The author's main purpose is to show how closely interwoven are the patterns obtained by all the widely different technics of securing an electrocardiographic tracing. The "standard" leads, the precordial leads, the unipolar leads and the epicardial leads in experimental animals are all expressions of the identical electrical phenomena and must therefore be interrelated. Dr. Hecht is at pains to link these close relationships. He achieves this aim with thoroughness and conciseness, though not always with the lucidity that one would wish. A selected bibliography of some 44 references is appended.

This text does not make easy reading. For proper assimilation much of it requires to be read, reread and pondered. The reader who is not thoroughly familiar with the significance of such terms as *instantaneous, modal* and *mean electrical axes, ventricular gradient,* or *vectorcardiogram,* will be well advised to study the glossary

at the back of the book before embarking on the text. For the author makes no allowance for the uninitiated. Indeed this text is clearly not for the beginner; it is more of value to knit up the knowledge of one who has already a good grasp of clinical electrocardiography.

H. J. L. M.

Practical Neurological Diagnosis, with Special Reference to the Problems of Neurosurgery. 4th Ed. By R. GLEN SPURLING, M.D. 268 pages; 15.5 × 23.5 cm. Charles C Thomas, Springfield, Illinois. 1950. Price, $5.00.

This book can be recommended without reservations. The author has fully achieved his goal, *"to present a simple account of the principles of neurological diagnosis."*

One of the most commendable of the many excellent features of this text consists of the lucid descriptions of the various procedures that make up the neurological examination. To add further to this, the author points out what is to be avoided in the execution of these procedures. For instance, he opposes the use of mydriatics as an aid to examining the fundi because it deprives one of "information concerning the pupils which may be of great diagnostic value." He points out that, "Leading questions, such as, 'Is that sharp?' or 'Is that cold?' should be avoided in the sensory examination." However, while one is warned with respect to the colloidal gold curve that "The syphilitic curve is frequently found in cerebrospinal fluid in which there is an excess of protein from any cause," the author still refers to a high first zone curve as a paretic curve, and a low first zone curve as syphilitic. I believe these terms imply a greater specificity than is present, and contradict the warning quoted above. The author rightfully advises that "Many patients with operable brain tumors have been robbed of every chance for recovery simply because they were unfortunate enough to have a positive blood serum or cerebrospinal fluid Wasserman reaction." These gems of clinical wisdom, of which this book has a good store, make up a significant part of its worthiness. To add another example, "Ankle-clonus," it is pointed out, "may occur in highly nervous individuals after prolonged illness, and it may also occur after severe muscular exertion. It is therefore not invariably a sign of organic disease." I have not infrequently seen isolated ankle-clonus confuse an examiner because it was considered "organic" in origin.

The author has really succeeded in integrating the anatomical and physiological data with the clinical data. Such an arrangement should be very helpful to the beginner. The discussion of the cerebral cortex is particularly good, for no sacrifice of the currently accepted dynamic processes of the cortex has been made in order to stress their clinical application. Another example of excellent condensation is the listing of the spinal motor levels on the basis of muscle groups rather than individual muscles with the great amount of overlapping that might confuse the beginner. All in all this is an ideal book for students, for in addition to teaching it does so in such an uncomplicated manner that the student might doubt that he is learning much because of the pleasant style. If a student does not learn a great deal that is basic from this book, then he is a student of only doubtful quality.

H. A. T.

Tuberculosis and Other Problems of Pediatrics (the Abraham Flexner Lectures—Series Number 10). By ARVID WALGREN, M.D., Professor of Pediatrics, The Royal Caroline Medical Institute, Stockholm, Sweden. 108 pages; 14 × 21 cm. Published for Vanderbilt University by The Williams and Wilkins Company, Baltimore, Md. 1950. Price, $2.25.

This little volume presents the five lectures which Dr. Walgren gave at the Vanderbilt University, School of Medicine as the tenth series of the Abraham Flexner Lectures. A brief explanation is provided as to how this endowed lectureship operates.

The first lecture in this series is on general trends in combating tuberculosis in childhood. It tells of how infection is prevented and how it is managed once it occurs. The author discusses methods used for the prevention of infection and the methods used for prevention of disease once infection has taken place. Lastly he describes the methods used in the treatment of the disease as they are applied in Sweden.

The second lecture concerns BCG vaccination. The author states that: (1) BCG is harmless and causes no real discomfort to the individual; (2) the inoculation must be performed in such a way and with such a dose as to produce tuberculin-sensitivity; (3) the intracutaneous method of vaccination which was introduced in 1927 has proved to be a thoroughly satisfactory method; (4) immunity produced is relative, but thanks to the fact that airborne virulent infection is usually slight it is nevertheless sufficiently strong as a rule to form a satisfactory protection against the immediate consequences of virulent primary infection; (5) the duration of immunity is different in different individuals, but usually lasts for five years or more; (6) the results so far obtained with adequately performed BCG vaccination are very encouraging when the immunity has had time to develop after the inoculation and when the virulent infection has occurred after the vaccinated individual has acquired sensitivity to tuberculin.

The third lecture records the author's experience with 1,000 cases of erythema nodosum. Tuberculosis is by far the commonest cause of erythema nodosum. The relation of erythema nodosum to other nontuberculous conditions is discussed as well as its occurrence following the administration of tuberculin and of sulfathiazole.

The fourth lecture describes how the problem of illegitimate children is handled in Sweden. Because of the high illegitimacy rate and because of the comparatively higher death rate among illegitimate children vs. legitimate children special laws and technics have been developed to offset the normally low birth rate of this country.

The last lecture is on hypertrophic pyloric stenosis. There is first a discussion of the theory regarding etiology and pathogenesis of the disease. Then the author describes the medical management as used by him. He prefers this to surgery and states that under ideal conditions proper medical management can be as successful as surgery. He adds, however, that unless ideal conditions exist, surgery should not be too long delayed if a trial of medical measures proves unsatisfactory.

L. V. B.

BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Biochemistry of Inositol: A Critical Examination of the Literature. Mellon Institute Bibliographic Series Bulletin No. 6. By EDWARD R. WEIDLEIN, JR. 53 pages; 23 × 15 cm. (paper-bound). 1951. Mellon Institute of Industrial Research, University of Pittsburgh, Pittsburgh, Pennsylvania. Complimentary copy on request.

Cancer As I See It. By HENRY W. ABELMANN, M.D. 100 pages; 20.5 × 14 cm. 1951. Philosophical Library, New York. Price, $2.75.

Cornell Conferences on Therapy—Volume IV. Edited by HARRY GOLD, M.D., Managing Editor; DAVID P. BARR, M.D., MCKEEN CATTELL, M.D., FRANK GLENN, M.D., WALTER MODELL, M.D., and GEORGE READER, M.D. 342 pages; 21 × 14 cm. 1951. The Macmillan Company, New York. Price, $3.50.

Diabetes Guide Book for the Physician. 79 pages; 17 × 12.5 cm. (paper-bound). 1950. American Diabetes Association, Inc., New York.

Dimensional Analysis for Students of Medicine. By HAROLD A. ABRAMSON, M.D., Assistant Clinical Professor of Physiology, Columbia University, etc. 41 pages; 23 × 15 cm. (paper-bound). 1950. The Josiah Macy, Jr. Foundation, New York. Price, $1.00 each; 6 to 25, 75¢ each; over 25, 50¢ each.

Die Entzündungsbestrahlung. By DR. MED. HABIL. R. GLAUNER. 189 pages; 24.5 × 17.5 cm. 1951. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, $4.45.

Eternal Eve: The History of Gynaecology and Obstetrics. By HARVEY GRAHAM. 699 pages; 23.5 × 15 cm. 1951. Doubleday & Company, Inc., Garden City, N. Y. Price, $10.00.

Heart Disease: Its Diagnosis and Treatment. By EMANUEL GOLDBERGER, B.S., M.D., Associate Attending Physician, Montefiore Hospital, New York, etc. 651 pages; 24 × 15.5 cm. 1951. Lea & Febiger, Philadelphia. Price, $10.00.

An Introduction to Universal Serologic Reaction in Health and Disease. By REUBEN L. KAHN, D.Sc., University of Michigan Medical School and Hospital, Ann Arbor, Michigan. 159 pages; 20.5 × 25 cm. 1951. The Commonwealth Fund, New York. Price, $3.50.

Lehrbuch der Röntgendiagnostik. By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL and E. UEHLINGER. 1046 pages; 28.5 × 20 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, $19.50.

Leitfaden der Blutmorphologie. By LYDIA SCHUDEL. 51 pages; 24 × 17 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, $3.50.

Man Is a Microcosm. By J. A. V. BUTLER. 162 pages; 21.5 × 14.5 cm. 1951. The Macmillan Company, New York. Price, $3.00.

The Microkaryocytes, the Fourth Corpuscles and Their Functions. By K. G. KHOROZIAN, A.B., M.S., M.D. 969 pages; 22.5 × 14.5 cm. 1951. Meador Publishing Company, Boston. Price, $12.00.

Occupational Factors in the Aetiology of Gastric and Duodenal Ulcers, with an Estimate of Their Incidence in the General Population—Medical Research Council Special Report Series No. 276. By RICHARD DOLL and F. AVERY JONES, with the assistance of M. M. BUCKATZSCH. 96 pages; 23.5 × 15 cm. (paper-bound). 1951. His Majesty's Stationery Office, London. Price, 2s. 6d. net.

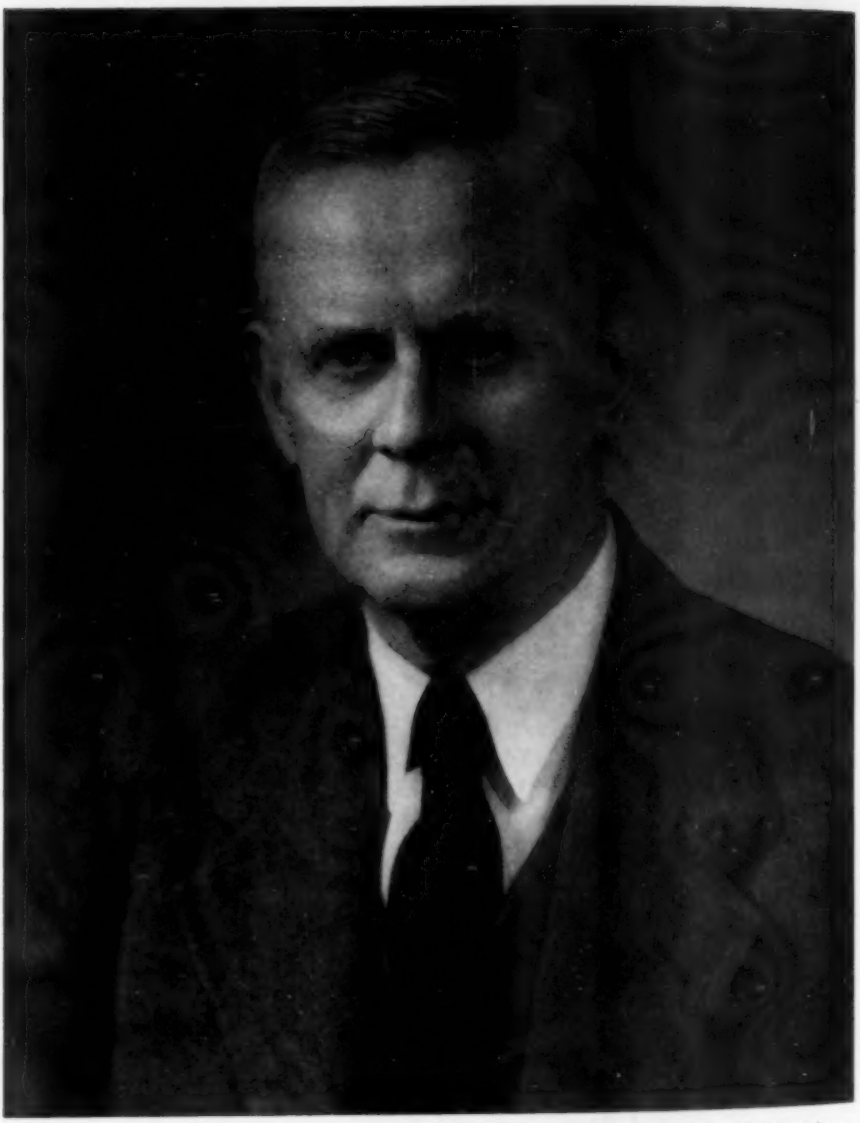
Pain and Its Problems. Edited by SIR HENEAGE OGILVIE, K.B.E., D.M., M.CH., F.R.C.S., and WILLIAM A. R. THOMSON, M.D. 194 pages; 22 × 14.5 cm. 1950. The Blakiston Company, Philadelphia. Price, $3.00.

Paracelsus: Magic Into Science. By HENRY M. PACHTER. 360 pages; 21.5 × 14 cm. 1951. Henry Schuman, Inc., New York. Price, $4.00.

Perspectives in Human Malnutrition: A Contribution to the Biology of Diseases from a Clinical and Pathological Study of Chronic Malnutrition and Pellagra in the African. By JOSEPH GILLMAN, D.Sc., M.D., B.Ch., and THEODORE GILLMAN, M.Sc., M.B., B.Ch., Departments of Physiology and Anatomy, Medical School, University of the Witwatersrand, etc. 584 pages; 26.5 × 18 cm. 1951. Grune & Stratton, Inc., New York. Price, $18.00.

Somatic and Psychiatric Treatment of Asthma. Edited by HAROLD A. ABRAMSON, M.D., Associate Physician and Chief, Allergy Clinic, The Mount Sinai Hospital, New York, etc. 751 pages; 24 × 15.5 cm. 1951. The Williams & Wilkins Company, Baltimore. Price, $11.00.

Textbook of Physiology and Biochemistry. By GEORGE H. BELL, B.Sc., M.D. (Glasg.), F.R.F.P.S.G., F.R.S.E., Professor of Physiology in the University of St. Andrews at University College, Dundee; J. NORMAN DAVIDSON, M.D., D.Sc. (Edin.), F.R.F.P.S.G., F.R.I.C., F.R.S.E., Gardiner Professor of Physiological Chemistry in the University of Glasgow, etc., and HAROLD SCARBOROUGH, M.B., Ph.D. (Edin.), F.R.C.P.E., Professor of Medicine in the Welsh National School of Medicine of the University of Wales and Director of the Medical Unit in the Royal Infirmary, Cardiff, etc.; with a foreword by ROBERT C. GARRY, M.B., D.Sc. (Glasg.), F.R.F.P.S.G., F.R.S.E., Regius Professor of Physiology in the University of Glasgow. 918 pages; 24.5 × 17 cm. 1950. The Williams & Wilkins Company, Baltimore. Price, $9.00.



MAURICE C. PINCOFFS, M.D., M.A.C.P., President, American College of Physicians

Maurice C. Pincoffs, M.D., M.A.C.P., President, American College of Physicians

Maurice C. Pincoffs—B.S., M.D., University Hospital, Baltimore 1, Md. Born, August 6, 1886, Chicago, Ill. B.S., 1909, University of Chicago; M.D., 1912, Johns Hopkins University School of Medicine; Assistant in Anatomy, University of Chicago 1910; Research Assistant, Department of Pharmacology, Johns Hopkins University School of Medicine 1915–1917; Instructor in Medicine, Johns Hopkins University School of Medicine 1919–1921; Professor of Medicine and Head of the Department, since 1922, University of Maryland School of Medicine; Assistant to the President, University of Maryland, for Medical Affairs, 1949–1950; Member, since 1942, Maryland State Board of Health; Chairman, Committee on Medical Care of the Maryland State Planning Commission, since 1941; former Member, Medical Advisory Committee to the Secretary of War 1947–1948; former Member Armed Forces Medical Advisory Committee to the Secretary of Defense, 1949–1951; Member of the Council of the Medical and Chirurgical Faculty of Maryland; Editor, since 1932, "Annals of Internal Medicine."

Captain, Medical Corps, U. S. Army, 1917–1919; Colonel, Medical Corps, U. S. Army, 1942–1946; Chief Consultant, USAFFE; Chief, Preventive Medicine, AFPAC; Awarded Distinguished Service Cross, Legion of Merit with Oak Leaf Cluster (U. S.); Croix de Guerre with palm (France).

Physician in Chief, University Hospital, Baltimore, Md.; Consulting Physician, Mercy Hospital, Baltimore, Md.; former President American Clinical and Climatological Association; Member, Association of American Physicians; Member, Cosmopolitan Club; Member, Eclat Club; Member, Medical and Chirurgical Faculty of Maryland; former President, Mental Hygiene Society of Maryland; Fellow, American Medical Association; Diplomate, American Board of Internal Medicine; Author of numerous articles and several chapters of Medical Systems.

Dr. Pincoffs was elected a Fellow of the American College of Physicians in 1923 and a Master in 1947. He served as the College Governor for the State of Maryland from 1926–29 and as a Regent from 1929–32, First Vice President, 1932–33, and thereafter as a Regent ex officio by reason of being the Editor of the "Annals of Internal Medicine," until 1950, when he was made President-Elect.

Dr. Pincoffs served as the General Chairman of the Fifteenth Annual Clinical Session of the College held in Baltimore in 1931. He has served on many Committees of the College, and under his Editorship, the official journal of the College, the "Annals of Internal Medicine," has attained an outstanding position in the field of Internal Medicine.

T. Grier Miller, M.D., F.A.C.P., President-Elect, American College of Physicians

T. Grier Miller, M.D., F.A.C.P., President-Elect, American College of Physicians

T. Grier Miller—A.B., M.D., LL.D., 133 S. 36th Street, Philadelphia 4, Pa. Born, September 18, 1886, Statesville, N. C. A.B., 1906, University of North Carolina; M.D., 1911, University of Pennsylvania School of Medicine; LL.D., 1943, University of North Carolina. Interne, 1911–13, Hospital of the University of Pennsylvania; Associate in Medicine, 1916–28, Assistant Professor of Medicine, 1928–34, Professor of Clinical Medicine, 1934–46, Professor of Medicine, 1946 to date, University of Pennsylvania School of Medicine; Chief, Gastro-intestinal Section, 1928–48, and Consultant to Gastro-intestinal Section, 1948 to date, Hospital of the University of Pennsylvania; formerly Consulting Physician to Friends, Abington Memorial and Chestnut Hill Hospitals; served in the Medical Corps of U. S. Army during World War I; former Vice President, Pathological Society of Philadelphia; former Treasurer, former Vice President and presently President, College of Physicians of Philadelphia; former President, Philadelphia County Medical Society; former President, American Clinical and Climatological Association; President, American Gastro-enterological Association; Member, Association of American Physicians, Medical Society of the State of Pennsylvania, and Fellow, American Medical Association; Member, Medical Fellowship Board, National Research Council, 1941 to date; Diplomate, American Board of Internal Medicine and a Member of the certifying Sub-specialty Board in Gastro-enterology; Author of numerous articles and chapters to medical systems, especially in the field of Gastro-enterology and Nutrition.

Dr. Miller became a Fellow of the American College of Physicians in 1930 (Life Member, 1944), was elected a Regent of the College in 1946 and thereafter served on numerous Committees of the College. He was made President-Elect in 1951, and will serve as President, 1952–53.

COLLEGE NEWS NOTES

The St. Louis Annual Session

The 32nd Annual Session of the American College of Physicians was held at St. Louis, Mo., April 9–13, 1951, under the Presidency of William S. Middleton, M.D., Madison, Wis., and the General Chairmanship of Ralph A. Kinsella, M.D., St. Louis, Mo. Among the highlights of the meeting were two addresses, including the Convocation Oration, by Sir John Parkinson, F.R.C.P., of London, England, on whom an Honorary Fellowship, second in the history of the College, was conferred; the James D. Bruce Memorial Lecture on Preventive Medicine by Rolla Eugene Dyer, M.D., Director of Research, Emory University, and former Director, National Institutes of Health, of Atlanta, Ga., on whom the James D. Bruce Memorial Medal for 1951 was conferred; the conferring of a Mastership upon Ernest E. Irons, M.D., Chicago, a former President of the American College of Physicians and of the American Medical Association; the conferring of the Alfred Stengel Memorial Award upon George Morris Piersol, M.D., Philadelphia, who for the past twenty-five years has been the Secretary-General of the College.

A condensed, sound motion picture (Teleclinic) of the Session was made and will be available for showing at Regional Meetings of the College and other gatherings of physicians. Certain of the Panel Discussions were recorded for like purposes. Hospital clinics were televised in color from the St. Louis City Hospital to the Kiel Auditorium as an integral part of the program. The "Teleclinic" motion picture was underwritten by Wyeth, Inc., of Philadelphia; the color television, by Smith, Kline and French, of Philadelphia.

The Officers, Regents and Governors of the College presented to Mr. Edward R. Loveland, Executive Secretary for the past twenty-five years, a sterling English-style cocktail set and tray, appropriately engraved, and to Miss Pearl M. Ott, Executive Assistant and Secretary to Mr. Loveland for the past twenty-five years, a handsome gold pin and a $500.00 Government bond.

Three hundred, twenty-six physicians were inducted to Fellowship at the Convocation. Four hundred new Associates were admitted since the previous Annual Session.

Maurice C. Pincoffs, M.D., Baltimore, Md., Professor of Medicine and Head of the Department, University of Maryland School of Medicine, was inducted as President; T. Grier Miller, M.D., Philadelphia, Pa., Professor of Medicine, University of Pennsylvania School of Medicine, and President of the College of Physicians of Philadelphia, was elected President-Elect; Richard A. Kern, M.D., Philadelphia, Pa., Professor of Medicine and Head of the Department, Temple University School of Medicine, and Consultant in Medicine to the Surgeons General of the U. S. Army and U. S. Navy, was elected Secretary-General, succeeding George Morris Piersol, M.D., Philadelphia. Other elections include: LeRoy H. Sloan, M.D., Chicago, Ill., First Vice President; Walter B. Martin, M.D., Norfolk, Va., Second Vice President; Howard P. Lewis, M.D., Portland, Ore., Third Vice President; William D. Stroud, M.D., Philadelphia, Pa., re-elected Treasurer; Marian A. Blankenhorn, M.D., Cincinnati, Ohio, Asa L. Lincoln, M.D., New York, N. Y., J. Owsley Manier, Nashville, Tenn., Walter L. Palmer, M.D., Chicago, Ill., Wallace M. Yater, M.D., Washington, D. C., and Dwight L. Wilbur, M.D., San Francisco, Calif., Regents of the College. The personnel of the Board of Governors appears elsewhere in this issue.

33rd Annual Session, 1952

The 33rd Annual Session of the College will be held in Cleveland, Ohio, April 21–25, 1952. President Maurice C. Pincoffs will be in charge of the program of Morning Lectures and General Sessions. Roy W. Scott, M.D., Cleveland, has been appointed by the Board of Regents as General Chairman, in charge of the program of Panel Discussions, Hospital Clinics, Color Television, and general arrangements.

The Board of Regents has already selected Atlantic City, N. J., for the site of the 34th Annual Session, 1953, to be held during the week of April 13–17.

Elections to Membership, A. C. P.

The following elections to membership in the College took place at St. Louis, April 8, 1951:

Associates

Peter Amazon ..... Bronx, N. Y.
George Sigurd Balfour ..... Lethbridge, Alta., Can.
Thomas Stewart Barnes ..... Dallas, Tex.
George Jay Baylin ..... Durham, N. C.
Joseph P. Belber ..... Oakland, Calif.
Bernard Harvey Berman ..... Washington, Pa.
Lynn Allen Bernard ..... Houston, Tex.
Leonidas Harris Berry ..... Chicago, Ill.
Philip Kramer Bondy ..... Atlanta, Ga.
Robert Irving Boyd ..... Pasadena, Calif.
Frank Reid Brown ..... Greensboro, N. C.
Robert A. Bruce ..... Seattle, Wash.
DeWitt Kinne Burnham ..... San Francisco, Calif.
Nathaniel Oglesby Calloway ..... Chicago, Ill.
Woodrow Marcellus Campion ..... Liberal, Kans.
Elmer L. Caveny ..... M.C., U. S. Navy
Jerome Chamovitz ..... Sewickley, Pa.
Nathaniel Abraham Cohen ..... Forest Hills, N. Y.
Edwin Morton Cohn ..... Philadelphia, Pa.
Harold Cohn ..... Brooklyn, N. Y.
Robert Rayner Commons ..... Beverly Hills, Calif.
James J. Conn ..... Columbus, Ohio
William Rhett Craig, Jr. ..... Greenville, S. C.
Milton Cutler ..... Hammonton, N. J.
Gerald Birch Demarest ..... Westfield, N. J.
Maurice Dunn ..... Gulfport, Miss.
Samuel Dvoskin ..... New York, N. Y.
Robert Edward Eckardt ..... New York, N. Y.
Albert Eckstein ..... Phoenix, Ariz.
Arthur Francis Edwardes ..... Los Angeles, Calif.
Alban W. Eger ..... Washington, D. C.
Jack Langohr Eisaman ..... Bluffton, Ind.
Harold Victor Ellingson ..... M.C., U. S. Air Force
Frank Libman Engel ..... Durham, N. C.
Albert Charles England, Jr. ..... Boston, Mass.
David Sproul Evans ..... M.C., U. S. Air Force

Robert Magwood Fawcett	Devils Lake, N. D.
David Feldman	St. Louis, Mo.
Giles Franklin Filley	Saranac Lake, N. Y.
Malvin Finkelstein	Jersey City, N. J.
John Taylor Montague Fraser	Ottawa, Ont., Can.
Irving Freeman	Baltimore, Md.
Vincent Edward Friedewald	Big Spring, Tex.
Ernest Oskar Friedlander	Togus, Maine
Harry Friedman	New York, N. Y.
George E. Gates	South Bend, Ind.
Charles Louis Gilbert	New York, N. Y.
Robert Lincoln Gilbert	La Crosse, Wis.
William Henry Glass	Hartford, Conn.
John Godfrey	White River Junction, Vt.
Ralph Goldman	Los Angeles, Calif.
Robert Jarvis Gould	Portland, Ore.
John Joseph Hammond	St. Louis, Mo.
Robert Paul Hardwig	Waverly, Iowa
Howard Yeager Harris	Kingston, Pa.
John Roger Haserick	Cleveland, Ohio
Robert Galbraith Heath	New Orleans, La.
Milton R. Hejtmancik	Galveston, Tex.
Emanuel Hellman	New York, N. Y.
Philip Edward Henig	New York, N. Y.
William Lane Hewitt	Los Angeles, Calif.
Robert Sexton Higdon	M.C., U. S. Army
Mark Timothy Hoekenga	La Lima, Cortes, Honduras
Charles John Hornisher	M.C., U. S. Army
Robert Palmer Howard	Montreal, Que., Can.
Joe Wiseman Howland	Rochester, N. Y.
Bernard Hulbert	St. Louis, Mo.
Laurence Mercer Hursh	M.C., U. S. Army
Myles Henry Illingworth	Springfield, Mass.
Saul Jarcho	New York, N. Y.
Blocker Howe Joslin	Minneapolis, Minn.
Bernard S. Kahn	New York, N. Y.
Leonard Kent	San Fernando, Calif.
Andrew Kerr, Jr.	New Orleans, La.
Ross Conklin Kory	Nashville, Tenn.
Sidney Ourin Krasnoff	Philadelphia, Pa.
Edward Charles Kunkle	Durham, N. C.
David Milton Kurschner	New York, N. Y.
Harry Clayton Leavitt	Seattle, Wash.
Thomas Norwood Lide	Winston-Salem, N. C.
Ellsworth LaVerne Lindley	Cedar Rapids, Iowa
Raymond Davidson Little	Wharton, Tex.
John Swepson Llewellyn	Louisville, Ky.
Earl Lavon Loyd	Jefferson City, Mo.
Doss Owen Lynn	M.C., U. S. Army
James Charles Mankey	Minneapolis, Minn.
Moe Price Margolies	Philadelphia, Pa.
Samuel Preston Martin	Durham, N. C.
Hugh Mathis Mason	Los Angeles, Calif.

Jacob David **Matis** ..... New York, N. Y.
Paul Emil **Mattman** ..... Detroit, Mich.
Howard McDowell **McCue, Jr.** ..... Richmond, Va.
Charles Ralph **Messeloff** ..... New York, N. Y.
John **Meyers** ..... Worcester, Mass.
Paul Floyd **Miner** ..... Boise, Idaho
James Stephen **Missett** ..... Hartford, Conn.
Aaron **Moldover** ..... Brooklyn, N. Y.
Donald Spencer **Munroe** ..... Vancouver, B. C., Can.
Robert Stuart **Nelson** ..... M.C., U. S. Army
Harold Bertram **Orenstein** ..... Brooklyn, N. Y.
George Lord **Parkin** ..... Dayton, Ohio
Marcel **Patterson** ..... Boston, Mass.
Thomas Edward **Pederson** ..... Jamestown, N. D.
William Harry **Perloff** ..... Philadelphia, Pa.
Erwin Emanuel **Peters** ..... Monroe, Wis.
John Bernard **Pfeiffer, Jr.** ..... Durham, N. C.
Charles **Pokorny** ..... Long Beach, Calif.
Albert Abbot **Pollack** ..... New York, N. Y.
Harold Sackett **Pond, Jr.** ..... Stroudsburg, Pa.
John Stephenson **Powers, Jr.** ..... Kingsport, Tenn.
Andrew Gabriel **Prandoni** ..... Washington, D. C.
William Donald **Preston** ..... M.C., U. S. Air Force
Herman **Reinstein** ..... Brooklyn, N. Y.
Maurice **Rich** ..... Miami, Fla.
Norbert Joseph **Roberts** ..... New York, N. Y.
Robert Boyd **Rodman** ..... Wilmington, N. C.
Frederick Edward **Rose** ..... Belleville, Ill.
Herbert **Rosenbaum** ..... Detroit, Mich.
Sidney Benjamin **Rosenbluth** ..... New York, N. Y.
Philip Wayne **Rothrock** ..... Lafayette, Ind.
Joseph E. **Rothschild** ..... Dallas, Tex.
Julius Johnson **Sachs** ..... Brooklyn, N. Y.
Dwight Santiago-**Stevenson** ..... San Juan, P. R.
Theodore Herbert **Sattler** ..... Yankton, S. D.
Eric Dutton **Savage** ..... South Orange, N. J.
Sydney **Schiffer** ..... San Antonio, Tex.
Theodore Benoni **Schwartz** ..... Durham, N. C.
Stephen **Sewell** ..... Spring Lake, N. J.
John Frederick **Shaul** ..... M.C., U. S. Navy
Paul Albert **Shaw** ..... Wilmington, Del.
Daniel Joseph **Sheehan** ..... M.C., U. S. Army
Herbert **Shulman** ..... Waterloo, Iowa
Ruben **Snyderman** ..... Pittsburgh, Pa.
Edward Lee **Stevenson** ..... The Dalles, Ore.
Irving Lewis **Stutz** ..... Pittsburgh, Pa.
Carroll Steiner **Svare** ..... M.C., U. S. Army
Ross Van Valkenburg **Taylor** ..... Jackson, Mich.
Benjamin B. **Teitelbaum** ..... Cleveland, Ohio
Alexander Theodore **Thom** ..... Montreal, Que., Can.
James Lynn **Turner** ..... Oakland, Calif.
Henry Lewis **Valk** ..... Winston-Salem, N. C.
Arthur Edward **Varden** ..... San Bernardino, Calif.

Charles James Wallace, Jr.	Sacramento, Calif.
Albert Samuel Warren	Lexington, Ky.
Harold Draper Warren	Brooklyn, N. Y.
William Edward Watts	Seattle, Wash.
Joseph Weinrib	Montgomery, Ala.
Eugene Weiss	South Bend, Ind.
Arthur Robert Wertheim	Kew Gardens, N. Y.
Abraham George White	Forest Hills, N. Y.
George Wyman Willison	Evansville, Ind.
Henry Edward Wilson	Evanston, Ill.
Russell Howard Wilson	St. Paul, Minn.
Stewart McKee Wilson	Rogers, Ark.
Joseph Alcantara Winn	New York, N. Y.
Lester Eugene Wold	Fargo, N. D.

Fellows

Hyman Alexander	New York, N. Y.
Rudolph Angell	Rochester, N. Y.
Leslie Robert Angus	Devon, Pa.
Robert Nerces Armen, Sr.	Altoona, Pa.
Charles Dorsey Armstrong	Menlo Park, Calif.
Daniel Hill Autry	Little Rock, Ark.
Robert Earl Beamish	Winnipeg, Man., Can.
Morton Emmett Berk	Honolulu, T. H.
Rudolph Berke	Flushing, N. Y.
Robert Birchall	New Orleans, La.
Milton Edward Bobey	Cleveland, Ohio
Joel Thompson Boone	Washington, D. C.
Harry J. Borson	Berkeley, Calif.
John Zimmerman Bowers	Salt Lake City, Utah
Herbert Charles Breuhaus	Chicago, Ill.
Ward Wright Briggs	Wilmington, Del.
Morris Harold Brodkey	Omaha, Nebr.
James Graham Bruce	Springfield, Mass.
Espey Farnsworth Cannon	Redlands, Calif.
Sandy Baxter Carter	Atlanta, Ga.
Richard Colbert Cecil	Richmond, Va.
William Nesbitt Chambers	Hanover, N. H.
Robert Kyun Hyun Charr	Philadelphia, Pa.
Clifford Burns Cherry	Los Angeles, Calif.
Edward Patterson Childs	New York, N. Y.
Stanley Cohen	New Orleans, La.
Seymour Lewy Cole	Los Angeles, Calif.
Ralph Robert Coleman	Charleston, S. C.
Lazarre John Courtright	San Francisco, Calif.
John William Crosson	Winnetka, Ill.
Martin Wheatley Davis	St. Louis, Mo.
Alfred Dudley Dennison, Jr.	Maplewood, N. J.
Eugene Joseph Des Autels	Hines, Ill.
William Michael Donohue	Houston, Tex.
Ellet Haller Drake	Detroit, Mich.
Robert Uriel Drinkard, Jr.	Wheeling, W. Va.

Edwin Mather Duvall ..... Long Beach, Calif.
James Frank Elliott ..... Edmonton, Alta., Can.
Herbert Jones Erwin, Jr. ..... St. Louis, Mo.
Oscar Feinsilver ..... Worcester, Mass.
Charles Louis Fincke ..... Stamford, Conn.
Carlos Albert Fish ..... Louisville, Ky.
Hyman Fisher ..... Tucson, Ariz.
Jerome Kearney Fisher ..... South Pasadena, Calif.
Louis James Fisher ..... La Canada, Calif.
Don Davis Flickinger ..... M.C., U. S. Air Force
William Thomas Foley ..... New York, N. Y.
Jarrett Harter Folley ..... Hanover, N. H.
Louis Michael Foltz ..... Louisville, Ky.
William Jesse Ford ..... Chicago, Ill.
Marcel J. Foret ..... Washington, D. C.
Kenneth Rushton Fourcher ..... New York, N. Y.
Herbert Stockton Gaskill ..... Indianapolis, Ind.
James Thomas Geddis ..... New York, N. Y.
David Gelfand ..... Philadelphia, Pa.
Victor Ginsberg ..... Brooklyn, N. Y.
Arthur Samuel Glushien ..... Pittsburgh, Pa.
Alfred Golden ..... Buffalo, N. Y.
Bernard Alvin Goldman ..... Harvey, La.
Wendell Brown Gordon ..... Pittsburgh, Pa.
Milton J. H. Grand ..... New York, N. Y.
Grant Ostrander Graves ..... Columbus, Ohio
Ralph Gillespie Greenlee ..... Temple, Tex.
Louis Greenwald ..... New York, N. Y.
Henry Arthur Grennan ..... Washington, D. C.
Carl Frederick Hammerstrom, Sr. ..... Jamestown, N. Y.
Harold Edward Hand ..... San Francisco, Calif.
Edward O'Neil Harper ..... Cleveland, Ohio
Francis French Harrison ..... Cooperstown, N. Y.
Frederick Hamilton Hathaway ..... Lincoln, Nebr.
Jack Murray Hayes ..... Bakersfield, Calif.
Albert Hanly Held ..... Beverly Hills, Calif.
Allison Burney Henderson ..... Detroit, Mich.
William Grafton Hersperger ..... Baltimore, Md.
Albert William Hilker ..... Eau Claire, Wis.
(Ng) William Hing ..... Flint, Mich.
Richards Holmes Hoffman ..... Santa Ana, Calif.
Raymond Francis Holden, Jr. ..... St. Louis, Mo.
DeWitt Heibsen Hotchkiss, Jr. ..... Houston, Tex.
Frederic Bernard House ..... Ann Arbor, Mich.
Arnold Iglauer ..... Cincinnati, Ohio
Richard Henry Jacques ..... Columbus, Ohio
Ralph J. Jones ..... Charleston, W. Va.
Benjamin Milton Kagan ..... Chicago, Ill.
Albert Bernard Katz ..... Philadelphia, Pa.
Francis Raymond Keating, Jr. ..... Rochester, Minn.
Gerald Tambling Kent ..... Cleveland, Ohio
Robert Bews Kerr ..... Vancouver, B. C., Can.
John McCrae Kilgour ..... Winnipeg, Man., Can.

Albert David Kistin	Washington, D. C.
Benjamin Osamu Kondo	Los Angeles, Calif.
Carl William Kumpe	Covington, Ky.
Charles Nance La Due	Dallas, Tex.
Leslie Holmes Layman	Louisville, Ky.
Julian Elliot Levi	Baltimore, Md.
Harry Samuel Levine	Brooklyn, N. Y.
Harold Levy	Brooklyn, N. Y.
Walter Charles Lobitz, Jr.	Hanover, N. H.
Elmer A. Lodmell	M.C., U. S. Army
Frederick Caspar Mackenbrock	Oakland, Calif.
Moses Jacques Madonick	New York, N. Y.
Samuel Newman Maimon	Dayton, Ohio
Frank Xavier Marino	New Orleans, La.
Edgar Frank Mauer	Los Angeles, Calif.
Wiley Thomas McCollum	Oklahoma City, Okla.
George Thomas McKean	Detroit, Mich.
Urho Robert Merikangas	M.C., U. S. Army
Nathan Mitchell	Brooklyn, N. Y.
Haywood Leland Moore	Brunswick, Ga.
Eusebius Jerome Murphy	New York, N. Y.
Marc James Musser, Jr.	Madison, Wis.
Harvey Lester Myers	Cedarhurst, N. Y.
Kinloch Nelson	Richmond, Va.
Harold Nicholas Neu	Omaha, Nebr.
Harvey Eleazar Nussbaum	Newark, N. J.
William Nyiri	Newark, N. J.
Ralph Chandler Parker, Jr.	M.C., U. S. Navy
Paul Bellmonte Patton	Morristown, N. J.
Robert Potashnick	St. Louis, Mo.
Alberto Prieto	New Orleans, La.
Frank Princi	Cincinnati, Ohio
Simon Propp	Albany, N. Y.
Moorman P. Prosser	Oklahoma City, Okla.
Herbert Lamont Pugh	M.C., U. S. Navy
Thomas Johnson Rankin	Wichita, Kans.
Francis Alexander Reed	Miami Beach, Fla.
William Page Reed	Larchmont, N. Y.
Charles Wolfe Rieber	Forest Hills, N. Y.
Harold Rifkin	New York, N. Y.
Charles James Roberts	Enid, Okla.
Edward Pier Roemer	Madison, Wis.
Oscar Alan Rose	New York, N. Y.
David Harry Rosenberg	Chicago, Ill.
William Rosenblatt	Wichita Falls, Tex.
Morris Sol Rosenblum	Youngstown, Ohio
Oscar Ferdinand Rosenow	Columbus, Ohio
Ludwig Theodore Rosenthal	Beverly Hills, Calif.
Harold Richard Rossmiller	Cleveland, Ohio
Owen Royce, Jr.	Milwaukee, Wis.
Chauncey Lake Royster	Raleigh, N. C.
Isadore Rudnikoff	Yonkers, N. Y.
Raymond Charles Ryan	Jamaica, N. Y.

Harold Saul Schiro ..... Cincinnati, Ohio
Paul Lawrence Shallenberger ..... Sayre, Pa.
Samuel Jacob Shane ..... Sydney, Nova Scotia, Can.
Leonard Shapiro ..... Brooklyn, N. Y.
Fred Ralph Shechter ..... Philadelphia, Pa.
David Eli Silberman ..... New York, N. Y.
Werner Simon ..... Minneapolis, Minn.
Martin Louis Singewald ..... Baltimore, Md.
William Walter Sittler ..... Chicago, Ill.
Joseph Sklaver ..... Waterbury, Conn.
Kazimer Bogar Skubi ..... Seattle, Wash.
Norman George Sloane ..... Philadelphia, Pa.
Walker Stamps ..... Jacksonville, Fla.
Eugene Herman Sterne, Jr. ..... Cincinnati, Ohio
Joseph Blackburn Stevens ..... Greensboro, N. C.
Bernard Straus ..... Bronx, N. Y.
Charles Frederick Stroebel, Jr. ..... Rochester, Minn.
Morris Wistar Stroud, 3rd ..... Philadelphia, Pa.
Charles Woodrow Styron ..... Raleigh, N. C.
Nelson Moore Taylor ..... Grosse Pointe, Mich.
William Wood Taylor ..... Memphis, Tenn.
Robert Kenneth Colquhoun Thomson ..... Edmonton, Alta., Can.
Harvey John Tompkins ..... Arlington, Va.
Sidney Trubowitz ..... Brooklyn, N. Y.
John Edward Tysell ..... Eugene, Ore.
Robert William Vines ..... Denver, Colo.
Ernest James Vogel ..... Arlington, Mass.
Christopher G. Vournas ..... St. Louis, Mo.
Harold Lawrence Vyner ..... Baltimore, Md.
Alexander Minty Waldron ..... Ann Arbor, Mich.
Weldon Joseph Walker ..... M.C., U. S. Army
John Joseph Webster ..... New York, N. Y.
Harold Raleigh Weidner ..... Coldwater, Mich.
Duncan Whitehead ..... Brooklyn, N. Y.
Charles Fore Wilkinson, Jr. ..... New York, N. Y.
Leonard David Williams ..... Plainfield, N. J.
Herman Julius Wolff ..... St. Paul, Minn.
Julius Wolfram ..... Dallas, Tex.
Milton Marvin Yarmy ..... Youngstown, Ohio
John Dibert Yeagley ..... York, Pa.
Walter Archibald Younge ..... St. Louis, Mo.

The American Physicians Art Association will have an art exhibit during the A. M. A. Convention, which will be held in Atlantic City June 11–15, 1951. Any physician in the United States, Canada and Hawaii desiring to participate in this show should communicate with Dr. F. H. Redewill, Secretary, American Physicians Art Association, 760 Market Street, San Francisco 2, Calif.

The Mount Sinai Hospital, Miami Beach, Fla., will hold its First Annual Medical Seminar in Cardiovascular Diseases May 23–25, 1951. Among the guest speakers will be Dr. David I. Abramson, F.A.C.P., Chief, Peripheral Circulatory Clinic, Michael Reese Hospital, Chicago, and Dr. Samuel Bellet, F.A.C.P., Associate Pro-

fessor of Cardiology, University of Pennsylvania Graduate School of Medicine. Dr. Abramson's subjects are "Physiology and Physio-Pathology of Peripheral Vessels," and "Functional Vascular Diseases." Dr. Bellet's subjects will be "The Effect of Electrolyte Alterations on the Heart with Particular Reference to the Effect of Hyper- and Hypopotassemia," and "Treatment of Cardiac Arrhythmias with Particular Reference to the Use of Recent Therapeutic Agents."

Hugh W. Mahon Lectureship Inaugurated

The first endowed lectureship to honor a member of the Regular Army Medical Corps has been established. The Hugh W. Mahon Lectureship was inaugurated March 2, 1951, and the first lecture was given by Colonel Hugh W. Mahon, Medical Corps, Retired, at the Fitzsimons General Hospital, Denver, Colo. 185 civilian doctors and medical officers attended. Among the distinguished guests were Dr. James J. Waring, M.A.C.P., Professor Emeritus, University of Colorado School of Medicine, and Chairman of the Hugh W. Mahon Lectureship Trust Fund; Colonel Hugh R. Gilmore, F.A.C.P., representing the Surgeon General of the U. S. Army; Dr. Edgar Durbin, F.A.C.P., President of the Denver City and County Medical Society; and Dr. Ward Darley, F.A.C.P., Vice President and Dean of the Department of Medicine, University of Colorado School of Medicine.

The American Association of Railway Surgeons held its annual meeting in Chicago, April 3–5. Among the speakers not affiliated with a railroad were Dr. George C. Turner, F.A.C.P., Chicago, Ill., "Present Status of the Diagnosis and Treatment of Pulmonary Tuberculosis," and Dr. David E. Markson, F.A.C.P., Chicago, Ill., "Arthritis."

The University of California School of Medicine at Los Angeles will open its doors to the first class of students on September 19. The last day for filing applications is May 15, and requests for information should be addressed to the Office of Admissions, 405 Hilgard Avenue, Los Angeles 24, Calif. Dr. John S. Lawrence, F.A.C.P., is Head of the Department of Medicine.

The University of Wisconsin Medical School will again accept out-of-state students in its first-year classes up to a limit of 5 per cent of the total of the first year class for any given year. In making this announcement, Dr. William S. Middleton, F.A.C.P., Dean, pointed out that this action was possible due to the decline of veteran enrollment.

The Fifteenth Annual Postgraduate Institute of the Philadelphia County Medical Society was held April 24–27, 1951, under the general direction of Dr. Thomas M. Durant, F.A.C.P. Among the speakers were the following Fellows of the College: Dr. O. Spurgeon English, "The Rôle of the General Practitioner in Counseling Before and After Marriage"; Dr. Edward Weiss, "Iatrogenic Disorders"; and Dr. Henry L. Bockus, "Gastro-Intestinal Disorders of Functional Origin." A feature of the program was a Clinical-Pathological Conference, conducted by Dr. A. Reynolds Crane, F.A.C.P., Dr. Garfield G. Duncan, F.A.C.P., Dr. Hobart A. Reimann, F.A.C.P., and Dr. Charles M. Thompson, F.A.C.P.

Heard on the Symposium on Electrolyte Problems in General Practice were the following Fellows of the College: Dr. Louis A. Soloff, Dr. Samuel Bellet and Dr. Joseph R. Elkinton. Dr. Horst A. Agerty, F.A.C.P., participated in the Symposium on Miscellaneous Pediatrica. Dr. Joseph L. Hollander, F.A.C.P., and Dr. Joseph T. Beardwood, F.A.C.P., participated in the Symposium on Recent Therapeutic Advances. On the Panel Discussion, "The Management of Thrombo-embolic Disease" were Dr. Joseph B. Vander Veer, F.A.C.P., and Dr. Hugh Montgomery, F.A.C.P.

The new teaching hospital on Parnassus Heights, San Francisco, Calif., is to be named the "Herbert C. Moffitt Hospital" in honor of Dr. Herbert Charles Moffitt, Sr., F.A.C.P., who died February 5, 1951. Dr. Moffitt had been associated with the University of California School of Medicine since 1899, and, as Dean, directed the reorganization of the medical school and enlarged its facilities before World War I. The March issue of "The Bulletin" of the San Francisco Medical Society was a memorial issue to Dr. Moffitt.

Among the speakers at the meeting of the Eastern Section of the American Congress of Physical Medicine, held April 28 at the Philadelphia General Hospital, were Lieutenant Colonel Richard H. B. Dear, (MC), USA, (Associate), "Management of Korean Casualties with Physical Medicine"; Dr. Alvin B. C. Knudson, F.A.C.P., Washington, D. C., "Present Needs of the Veterans Administration in Physical Medicine and Rehabilitation"; and Dr. George Morris Piersol, M.A.C.P., Philadelphia, Pa., "What the Internist May Expect from Physical Medicine."

Dr. Louis J. Soffer, F.A.C.P., New York, N. Y., was among the visiting physicians participating in the Symposium on Lupus Erythematosus, held at the Center for Continuation Study at the University of Minnesota, April 5–6.

Dr. Vernon E. Powell, F.A.C.P., was recently advanced from Instructor to Assistant Professor of Clinical Medicine by the Emory University School of Medicine, Atlanta, Ga.

Dr. Samuel Cohen, F.A.C.P., New York, N. Y., was recently elected Vice Chairman of the Tuberculosis Sanatorium Conference of Metropolitan New York.

Among the visiting speakers on the program of the annual meeting of the Ohio State Medical Association, held in Cincinnati April 24–26, were Dr. Robert W. Wilkins, F.A.C.P., Boston, Mass., whose subject was "Treatment of Hypertension," and Dr. Paul R. Hawley, F.A.C.P., Chicago, Ill., who participated in a panel discussion on the small community hospital.

Colonel John Powell Williams, F.A.C.P., Professor of Clinical Medicine and Chief of the Medical Service at Veterans Administration Hospital, Richmond, Va., is in command of the Forty-fifth General Hospital, which has been reorganized and has become an Organized Reserve Training Unit in the Virginia Military District.

Rear Admiral Clyde W. Brunson, F.A.C.P., formerly Commanding Officer of the U. S. Naval Hospital, Philadelphia, Pa., has recently been appointed Medical Officer for the 13th Naval District, with headquarters at Seattle, Wash.

Dr. Anton S. Yuskis (Associate), San Diego, Calif., was elected the first President of the San Diego County Heart Association, an affiliate of the California Heart Association and the American Heart Association.

Dr. A. M. Ornsteen, F.A.C.P., Philadelphia, Pa., was recently promoted to Professor of Clinical Neurology by the University of Pennsylvania School of Medicine.

At the meeting of the Tioga County Medical Society in Owego, N. Y., on March 29, Dr. Milton J. Matzner, F.A.C.P., Brooklyn, N. Y., spoke on "Gastric Carcinoma." Dr. Matzner also read a paper entitled, "Supraampullary Carcinoma of the Duodenum with Successful Resection," before the National Gastroenterological Association at the New York Academy of Medicine on April 9, 1951.

Dr. George R. Herrmann, F.A.C.P., Galveston, Tex., Professor of Medicine, University of Texas School of Medicine, addressed the professional staff of Brooke Army Medical Center, Fort Sam Houston, Tex., on March 13, on "The Practical Significance of Recently Developed Cardiovascular Techniques to Medicine of Today and Tomorrow."

Among the guest speakers at the second annual Northern Virginia Clinical Assembly, which was sponsored by the Alexandria Medical Society on April 1, were Dr. Sol Katz, F.A.C.P., Washington, D. C., "Cough—Its Implications"; and Dr. Ephraim T. Lisansky (Associate), Baltimore, Md., "Psychosomatic Aspects of Cardiovascular Diseases."

Dr. Walter L. Palmer, F.A.C.P., Professor of Medicine, University of Chicago School of Medicine, and Regent of the College, was the guest speaker at the third annual meeting of the Spokane (Wash.) Society of Internal Medicine on March 31.

OBITUARIES

DR. PAUL JOHN HANZLIK

Paul John Hanzlik, Ph.G., Ph.C., A.B., M.A., M.D., F.A.C.P., was born in Shueyville, Iowa, July 24, 1885. He was a graduate of the University of Iowa College of Pharmacy, receiving his Ph.G. in 1902 and his Ph.C. in 1908. In 1908 he received his A.B. and in 1911 his M.A. from the University of Illinois. He received his M.D. in 1912 from the Western Reserve University School of Medicine. Following Dr. Hanzlik's graduation from medical school he became Demonstrator in Pharmacology at the Western Reserve University School of Medicine, where he rose through the various academic ranks to the post of Assistant Professor of Pharmacology. In 1921 he was appointed Professor of Pharmacology at the Stanford University School of Medicine. He held this post until the time of his death.

Dr. Hanzlik was the author of several hundred articles on pharmacology, therapeutics and other scientific subjects. His fields of particular interest were in the development of bismuth compounds and the salicylates. He was the first investigator to make a useful compound of bismuth which could be administered orally. Other absorbing subjects were the study of methenamine, cincophen, glycols, carbitols, colloidal dyes, cyanide antidotes, anti-convulsants and the bio-assay of digitalis. He was the author of numerous text books on pharmacology and therapeutics, and served for many years as Associate Editor of the "Journal of Pharmacology and Experimental Therapeutics."

In 1935 he became the Consulting Pharmacologist for the San Francisco Department of Public Health and the U. S. Department of Agriculture, and held these positions until about 1947. From 1929 to 1947 he served as Vice Chairman of the Council on Dental Therapeutics of the American Dental Association.

Dr. Hanzlik was elected a Fellow of the American College of Physicians in 1934. He was also a member of the American Society for Pharmacology and Experimental Therapeutics, the American Society of Biological Chemists, the American Physiological Society, the Society for Experimental Biology and Medicine, the American Association for the Advancement of Science and the California Academy of Medicine. He was also a Fellow of the American Medical Association, and served as Chairman of the Section on Pharmacology and Therapeutics in 1924. He was a member of Alpha Omega Alpha and Sigma Xi.

An outstanding pharmacologist of the classical school, Paul Hanzlik steadfastly maintained the soundest academic traditions. He carefully shunned that promotional distemper which has here and there crept into universities. He believed that sound work presented in dignified fashion rather than superficial outward flourishes was all important.

As a teacher he was precise and authoritative. It was said of him that his classroom experiments actually "worked"—a rare achievement. No one could be bored in conversation with Paul Hanzlik. His incisive mind went right to the core of a problem. He was devoid of insincerity and a friend was never disappointed if he went to him for advice. His life and work will endure for a long time in American medicine.

Dr. Hanzlik died on February 1, 1951. He is survived by his widow and two children, one of whom is a physician, Dr. Harold Hanzlik, of San Francisco.

DWIGHT L. WILBUR, M.D., F.A.C.P.,
Governor for Northern California

DR. EDWIN B. WINNETT

Edwin B. Winnett, Ph.G., M.D., Des Moines, Iowa, a Fellow of the American College of Physicians since 1936, died on December 8, 1950. Dr. Winnett was born in Carroll County, Iowa, February 18, 1884. He received the degree of Ph.G. at the Highland Park College of Pharmacy, Des Moines, in 1904, and his M.D. degree from Drake University College of Medicine in 1912.

Following his graduation, he served as Assistant in Medicine at the Drake University College of Medicine, and was Resident Physician at the Iowa Methodist Hospital. In 1916 he became Attending Physician at the Iowa Methodist Hospital and later Attending Physician at the Iowa Lutheran and Broadlawns Polk County Hospitals. In addition to membership in his County and State Medical Societies and the American Medical Association, Dr. Winnett served as Treasurer of the Iowa State Medical Society from 1932 to 1933. He was a Diplomate of the American Board of Internal Medicine.

Throughout his professional lifetime, Dr. Winnett was intensely interested in the problem of diabetes mellitus. A diabetic himself, his practice consisted largely of diabetics and he was zealous in educating his diabetic patients, the public and his fellow physicians, in the care and management of diabetes. These activities were continued long after his health began to fail.

B. F. Wolverton, M.D., F.A.C.P.,
Governor for Iowa

DR. WALTER FOX SMITH

Walter Fox Smith, M.D., F.A.C.P., Watertown, N. Y., died at 55 years of age on February 3, 1951, from a cerebral hemorrhage. He was suddenly stricken seven hours before his death.

Dr. Smith graduated from Cornell University with an A.B. degree in 1918 and received his M.D. from Cornell University Medical College in 1921. He served as an intern at the Bellevue Hospital in New York City. He practiced in Watertown since his internship and was one of the most highly respected physicians in Watertown. He was a member of the staff and Chief of the Medical Service of the House of the Good Samaritan and on the staff of the Mercy Hospital. He was also Consultant to the Medical Staff of the St. Lawrence State Hospital at Ogdensburg and a member of the Board of the Jefferson County Hospital.

Dr. Smith was a Past President of the Jefferson County Medical Society, a member of the New York State Medical Society and a Fellow of the American Medical Association. Dr. Smith had been a Fellow of the American College of Physicians since 1934. He was a member of the Black River Club, the Jefferson County Golf Club and the Clayton Yacht Club. He served as a Lieutenant in World War I.

Dr. Smith personified to the highest degree the characteristics of a personal physician. He had a very pleasing personality and always had the personal interest of the patient at heart. He had a very extensive practice in Watertown and the surrounding counties. He was very much beloved by his patients and friends who mourn his death very deeply. Surviving are his wife, Mrs. Adelaide Sherman Smith, and two children, Walter Sherman Smith and Grace Sherman Smith.

The City of Watertown has suffered a distinct loss in the death of Walter Fox Smith and the American College of Physicians has lost one of its loyal members.

Edward C. Reifenstein, Sr., M.D., F.A.C.P.,
Governor for Western New York

COMMANDER EDWIN PETERSON(MC), USN (Retired)

Edwin Peterson, M.D., F.A.C.P., was born in Rudiksvall, Sweden, August 18, 1887, and died in Denver, Colo., December 2, 1950. He received his degree of Doctor of Medicine at the University of Illinois College of Medicine in 1915, and interned at Cook County Hospital, Chicago. On November 26, 1917, he was appointed a Lieutenant (junior grade) in the Medical Corps of the U. S. Navy and served at the Naval Hospital, Great Lakes, Ill., and in the Virgin Islands during World War I. He had several tours of duty in Washington—Naval Medical School in 1923; the Naval Hospital, 1927–31; and from June 23, 1939, to March 2, 1940, Preventive Medicine Division, Bureau of Medicine and Surgery. He was placed on the retired list in 1940 for physical disability.

Commander Peterson specialized in internal and tropical medicine. He was a member of the American Society of Tropical Medicine, the Association of Military Surgeons, and the American Medical Association. He was made a Fellow of the American College of Physicians in 1931.

From the Bureau of Medicine and Surgery, U. S. Navy

DR. EDWARD INMAN WOLFE

Edward Inman Wolfe, M.D., F.A.C.P., Forty Fort, Pa., died February 16, 1951, after an illness of several months. He was born in Luzerne County, Pa., May 10, 1894, graduated from Jefferson Medical College of Philadelphia in 1917, and served during World War I as a Lieutenant in the Medical Corps of the United States Army.

Dr. Wolfe became associated with the Wilkes-Barre General Hospital in 1925, serving as Associate Physician until 1944 when he became Chief of the Medical Service, a post which he held until his death. He was a member of the Luzerne County and Lehigh Valley Medical Societies and of the Medical Society of the State of Pennsylvania. He was a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1931. He was also a member of Nu Sigma Nu and Alpha Omega Alpha Honorary Medical Societies.

American College of Physicians, Inc.

Balance Sheet, December 31, 1950

General Fund

Assets			*Liabilities*	
Current:			*Current:*	
Cash in Banks and on Hand		$ 85,867.96	Accounts Payable	$ 61.50
Accounts Receivable		11,289.20	Philadelphia Income Tax	52.73
American Air Lines		425.00		
Inventory of Keys, Pledges and Frames, at cost		733.40	*Deferred Income:*	
Accrued Income on Endowment Fund Investments		1,724.63	Advance Subscriptions, Annals of Internal Medicine, Volumes XXXIV to XXXXII	54,643.98
Accrued Income on General Fund Investments		704.35	1951 Exhibits, paid in advance	7,654.43
Investments at Book Value		266,485.35		
Insurance Deposit		555.00	*Restricted Funds:*	
Turner Subscription Agency		9.50	Income on James D. Bruce Fund Investments	395.83
Total Current Assets		$367,794.39	Income on A. Blaine Brower Fund Investments	375.00
			Reserve, 1950–51 Research Fellowship Fund	8,860.45
Deferred:			Reserve Fellowship, E. H. Estes, Jr.	2,161.29
Expenses, 32nd Annual Session	4,581.13			
Advertising, Volume XXXIV	308.25	4,889.38	Total Current Liabilities and Funds	$ 74,205.21
Fixed:				
College Headquarters:			General Fund, as annexed	412,298.25
Real Estate	112,882.32			
Less Depreciation	16,000.00	96,882.32		
Furniture and Equipment, at cost	11,360.85			
Less Depreciation	4,071.20	7,289.65		
Investment, Real Estate, 404–12 S. 42nd St.		9,647.72		
		$486,503.46		$486,503.46

Endowment Fund

Assets		*Liabilities*	
Current:		*Current:*	
Cash	$ 4,573.55	Endowment Fund, Principal	$333,833.42
Investments at Book Value	329,259.87	Accrued Income, Due to General Fund	1,724.63
Accrued Income on Investments	1,724.63		
	$335,558.05		$335,558.05

James D. Bruce Fund

Current:		*Current:*	
Investments in U. S. Government Bonds	$ 10,000.00	Principal	$ 10,000.00
Cash	395.83	Accumulated Income	395.83
	$ 10,395.83		$ 10,395.83

A. Blaine Brower Fund

Current:		*Current:*	
Investments in U. S. Government Bonds	$ 10,000.00	Principal	$ 10,000.00
Cash	375.00	Accumulated Income	375.00
	$ 10,375.00		$ 10,375.00

(Total Assets, $842,832.34) (Total Liabilities and Funds, $842,832.34)

Operating Statement

GENERAL FUND

For the Year Ended December 31, 1950

Balance, January 1, 1950		$ 339,668.68	
Add: Discounts Expired on Accounts Receivable		1.63	
		$ 339,670.31	
Less:			
Transfer to Endowment Fund of the Initiation Fees of Life Members	$ 5,005.00		
Research Fellowship Fund	15,700.00	20,705.00	$ 318,965.31
Add:			
Net Income for the Year Ended December 31, 1950, as Annexed			93,332.94
BALANCE, December 31, 1950			$ 412,298.25

ENDOWMENT FUND

For the Year Ended December 31, 1950

Principal Account, January 1, 1950		$ 307,199.64	
Add:			
Life Membership Fees Received during 1950	$ 17,561.67		
Transfer of Initiation Fees of New Life Members from General Fund	5,005.00		
Transfer from Dues Account, Subscription Account, etc.	238.33		
Net Profit on Endowment Fund Investments	3,828.78	26,633.78	$ 333,833.42

JAMES D. BRUCE FUND

For the Year Ended December 31, 1950

Principal Account, January 1, 1950		$ 10,000.00	
Add:			
Accumulated Income	$ 395.83		
1950 Accumulated Income	250.00		
	$ 645.83		
Less:			
James D. Bruce Memorial Award	125.00		
Alfred Stengel Award	25.00		
Transfer to Reserve—Fellowship Fund (Stengel)	100.00	395.83	$ 10,395.83

A. BLAINE BROWER FUND

For the Year Ended December 31, 1950

Principal Account, January 1, 1950		$ 7,500.00	
Add:			
April, 1950, Addition	$ 2,500.00		
Accumulated Income	156.25		
1950 Accumulated Income	218.75	2,875.00	$ 10,375.00
TOTAL, Endowment Funds			$ 354,604.25
TOTAL, All Funds			$ 766,902.50

General Fund

Summary of Operations for the Calendar Year 1950

Income:		
Annual Dues		$ 44,838.85
Initiation Fees		23,065.00
Subscriptions, ANNALS OF INTERNAL MEDICINE		125,629.57
Advertising, ANNALS OF INTERNAL MEDICINE		31,809.07
Income from Investments, General Fund (including Accrued)		14,517.39
Income from Investments, Endowment Fund (including Accrued)		14,534.67
Dividend on Perpetual Insurance Deposit		60.00
Sale of 1949 Directory		855.23
Southeastern Regional Meeting		115.55
Postgraduate Courses, Balance		4,432.14
Miscellaneous Income (Dr. W. G. Leaman's gift)		169.00
Rent—404–12 S. 42nd Street (net)		402.57
Profit on Sale or Maturity of Securities, General Fund		2,115.65
Profit on Equipment Traded In		37.50
Thirty-first Annual Session:		
Exhibits	$ 29,881.18	
Guest Fees	5,658.09	
Banquet Balance	397.40	
Boston Symphony Concert Balance	463.69	36,400.36
TOTAL INCOME		$ 298,982.55
Expenses:		
Salaries		$ 55,576.67
Communications		10,960.30
Office Supplies and Stationery		3,419.67
Printing		79,980.59
Traveling Expenses		13,992.21
Rent and Maintenance (including Annual Session)		3,341.56
College Headquarters—Maintenance, Taxes, Insurance, etc.		4,348.57
Conference Committee on Graduate Training in Medicine		108.50
Depreciation on College Headquarters Building		2,000.00
Depreciation on Furniture and Equipment		1,153.00
Keys, Pledges and Frames		258.30
John Phillips Memorial Prize		176.50
Investment Counsel Service and Security Custodian's Fee		865.00
Employees' Pension Fund		6,958.57
Collection and Exchange		17.29
Regional Meetings		5,562.85
James D. Bruce Memorial Award		236.50
Loss on Sale of Securities, General Fund		231.38
1950 Supplement		1,409.42
Preparation, James D. Bruce Memorial Medal		18.50
General Miscellaneous		2,260.87
Thirty-first Annual Session—Special Expenses:		
Auld Lang Syne Greeting Hour	$ 723.93	
Committee on Panels	1,839.86	
Committee on Publicity	1,140.42	
Committee on Ladies' Entertainment	1,665.67	
Committee on Clinics	114.34	
Committee on Entertainment	50.00	
Convocation	1,591.18	
Governors-Regents Dinner	535.11	
Registration	632.58	
Television Program	730.50	
Other Miscellaneous	3,749.77	12,773.36
TOTAL EXPENSES		$ 205,649.61
Net Income for 1950 Credited to General Fund		$ 93,332.94